3-17-87 BD-081 TXR-5822

R. Coberly

#3669A

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

005822

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Tebuthiuron, Toxicology Chapter of the Registration Standard

To: Mary C. Erumsele, PM-25
Registration Division (TS-767)

From: David L. Ritter, Toxicologist DLR 3-13-87
Review Section # 1
Toxicology Branch, HED (TS-769)

Through: R. Bruce Jaeger, Section Head 3/13/87
Review Section # 1
Toxicology Branch, HED (TS-769)

Through: Robert P. Zendzian, Ph.D. 3/18/87
Registration Standard Coordinator
Toxicology Branch, HED (TS-769)

Through: William Burnam, Deputy Chief 3/17/87
Toxicology Branch, (TS-769)

Attached is the Toxicology Chapter of the Registration Standard for Tebuthiuron.

cc
Rispin, SIS
Zendzian
Coberly

1 of 42

005822

TEBUTHIURON

N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea

TOXICOLOGY CHAPTER

REGISTRATION STANDARD

David L. Ritter, Toxicologist
Rev. Sec. # 1/Toxicology Branch
Hazard Evaluation Division TS-769C

1A

005822

Toxicology Chapter

Table of Contents

A. Toxicological Summary

Tebuthiuron is N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea. It is used as a herbicide on rangelands, irrigation ditchbanks and other noncrop areas. There are tolerances on grass, meat and milk.

The Four Hour LC_{50} of Tebuthiuron in rats was determined to be 3.696 mg/L. It is Category III for inhalation toxicity. No data are available on the acute oral or dermal toxicity or the eye or dermal irritation or sensitization.

In a subchronic feeding study, Harlan rats were offered diets containing 20, 50 or 125 mg/kg/day Tebuthiuron for three months. High animals showed decreased body weights, increased relative liver, kidney and gonad weights. High dose males also showed increased relative weights for spleen and prostate gland. The NOEL for relative organ weight ratios and histopathological effects is 50 mg/kg/day.

Tebuthiuron was applied dermally to White New Zealand rabbits, 6 hours per day at doses of 0 or 1000 mg/kg for 21 days. No signs of dermal toxicity or deaths were reported. The NOEL in this study was 1000 mg/kg.

Beagle dogs were given technical Tebuthiuron by capsule for one year at levels of 0, 12.5, 25.0 or 50.0 mg/kg bwt./day. The effects produced included increased liver ratios in high dose males and females; increased kidney ratios in high dose females, and increased thyroid ratios in high dose males without adverse histopathological findings. Clinical chemistry indicated a significant hepatotoxic effect at the high dose in both sexes. The overall NOEL based on these findings is 25.0 mg/kg/day.

Although chronic/oncogenicity studies in rats and mice were submitted, they were deemed to be of insufficient quality to support registration of Tebuthiuron. Therefore, a chronic rat study is required, and oncogenic studies are required in two species.

A teratology study in rats was submitted but was judged to be of insufficient quality to support registration. Therefore, teratology studies are required in two species.

In a multi-generation rat reproduction study, Harlan rats were offered diets containing 5, 10 or 20 mg/kg bwt./day of Tebuthiuron through two generations of offspring. No adverse effects were reported on reproductive performance at any level. NOEL = 20 mg/kg bw/day.

Tebuthiuron was negative in the Ames Assay with and without activation at levels of 5 to 5000 ug/plate.

Technical Tebuthiuron was slightly mutagenic (in the nonactivated assay) in a mouse lymphoma assay for the induction of forward mutations using the $TK^{+/-}$ cell line was sensitive to direct acting and activationdependant mutagens. It was not mutagenic in the activated assay.

Additional mutagenic studies are needed.

In a radio-label study Tebuthiuron was administered in the diet at 5 and 10 mg/kg bwt./day to lactating rats immediately post-partum for 48 hours. The dams were then milked and the amount of activity in the milk was determined. Technical Tebuthiuron and/or its metabolites appeared in the milk of lactating rats in a dose-related manner.

A guideline type metabolism study is needed.

Tebuthiuron is one of a class of substituted dimethylurea herbicides, others being Diuron and Monuron. Diuron was tested in mice and found to produce a significantly increased incidence of bladder carcinomas in male and female mice fed the material in the diet for two years at a level 357 mg/kg bwt./day. Monuron when offered in the diet male rats at levels of 37.5 and 75.0 mg/kg/day produced increased incidences of renal tubular cell adenomas and carcinomas and increased neoplastic nodules and carcinomas of the liver.

Linuron, a monomethylurea herbicide, produced testicular hyperplasia and adenomas, and interstitial cell tumors in male mice fed the material in the diet for one year at 18 and 89.3 mg/kg/day.

These findings strongly suggest that the urogenital tissues in rodents are especially sensitive to substituted methylurea compounds. The liver is also sensitive.

Based on these considerations, the Agency will not consider establishing further food tolerances pending receipt of the required chronic and oncogenicity studies. These must specifically address the question of potential oncogenic response in the urogenital system and the liver.

B. Toxicology Profile

81 Series Acute toxicity and Irritation Studies

81-1 Acute Oral

There are no valid studies available to assess the acute oral toxicity of technical Tebuthiuron. A study is required.

81-2 Acute Dermal

There are no valid studies available to assess the acute dermal toxicity of technical Tebuthiuron. A study is required.

81-3 Acute Inhalation

Sufficient data are available to assess the acute inhalation toxicity of technical Tebuthiuron (MRID 155730). The Four Hour LC_{50} in rats is > 3.696 mg/L; TOX Category III.

81-4 Primary Eye Irritation

There are no valid studies available to assess the primary eye irritancy of technical Tebuthiuron. A study is required.

81-5 Primary Dermal Irritation

There are no valid studies available to assess the primary dermal irritancy of technical Tebuthiuron. A study is required.

81-6 Dermal Sensitization

There are no valid studies available to assess the dermal sensitization potential of technical Tebuthiuron. A study is required.

81-7 Acute Delayed Neurotoxicity

No data are available on the acute neurotoxic effects of Tebuthiuron. This test is required only for compounds which are organophosphate inhibitors of cholinesterase, or related to such inhibitors or metabolites of such inhibitors. Tebuthiuron is not an organophosphate; therefore, a study is not required.

82 Series Subchronic Testing

82-1 Subchronic Oral

Sufficient data are available to satisfy the data requirement of a subchronic oral toxicity study in rats.

Harlan rats, 10/sex/dose, were offered diets containing 0, 400, 1000 or 2500 ppm (20, 50 or 125 mg/kg/day) technical Tebuthiuron for three months (MRID 0020662). High dose males and females showed decreased body weights, increased relative liver, kidney and gonad weights High dose males also showed increased relative weights for spleen and prostate gland. High dose males demonstrated slight to moderate vacuolization of the pancreatic acinar cells. Three of the high dose females demonstrated this lesion also.

The NOEL for relative organ weight ratios and histopathological effects in the pancreatic acinar cells is 1000 ppm (50 mg/kg/day).

A subchronic oral toxicity study in a non-rodent species is not required because there is a one year dog study available.

82-2 Subchronic Dermal (21-day)

Sufficient data are available to satisfy the requirement for subchronic dermal toxicity testing.

White New Zealand rabbits, 10/sex/dose, were exposed dermally to 0 or 1000 mg/kg of dry form technical Tebuthiuron to applied to 10% of the total body surface area for 21 days, 6 hours per day (MRID 149733). No signs of dermal toxicity or deaths were reported. 2/10 treated animals showed slight erythema which cleared by day 7. No systemic effects that could be attributed to dermal exposure were reported.

82-3 Subchronic Dermal (90-day)

A 90 day subchronic dermal toxicity study is not required because the existing registered end-uses should not result in repeated human skin contact for extended periods.

82-4 Subchronic Inhalation

A subchronic inhalation study is not required because the existing registered end-uses should not result in repeated inhahation contact for extended periods.

005822

82-5 Subchronic Neurotoxicity

No data are available on the subchronic neurotxicity of Tebuthiuron. Since an acute neurotoxicity study is not required, and since there is no evidence of neurotoxicity in mammalian species, this study is not required.

83 Series Chronic and Long Term Studies

83-1 Chronic Toxicity

Sufficient data are available to satisfy the requirement for a chronic study in a non-rodent species. A chronic study in a rodent species is required.

Beagle dogs, 4/sex/dose, were given technical Tebuthiuron by capsule for one year at levels of 0, 12.5, 25.0 or 50.0 mg/kg bwt./day (MRID 146801). The effects produced included increased liver ratios in high dose males and females; increased kidney ratios in high dose females, and increased thyroid ratios in high dose males. There were no adverse histopathological findings for these organs, however. Alanine transaminase and alkaline phosphatase values were significantly increased in the high dose males, as was alanine transaminase in the high dose females. This indicates a significant hepatotoxic effect at this level in both sexes. Increased thrombocyte counts in the High dose males throughout the study appear to be an isolated finding.

The overall NOEL based on organ weight ratios, increased serum alanine transaminase, alkaline phosphatase and increased thrombocyte counts is 25.0 mg/kg bwt./day.

83-2 Oncogenicity

Chronic/oncogenic studies in rats and mice were submitted but were found to be unacceptable to support registration of Tebuthiuron.

In a replicate study in mice, two groups of 60 males and 60 females served as concurrent controls and two groups of 40 animals per sex per dose each served as test groups (MRID 20717). The animals were offered diets containing 0, 400, 800 or 1600 ppm for two years (0.0, 57.1, 114.3 and 22.6 mg/kg bw/day). Several groups of animals failed to survive the test period in sufficient numbers to provide for adequate histopathologic and statistical analysis (less than the 25% recommended for an acceptable study). In addition, the control groups may have been inadvertently offered diets containing another chemical. Other deficiencies included: Unthriftiness, marked by a high incidence of nephritis, pneumonia and malignant lymphomas rendered detection of compound-related effects virtually impossible.

The results were the same in a replicate rat study similar to the mouse study above (MRID 20714): inadequate survival (less than 25% in some groups); unthrifty animals as evidenced by emaciation, pneumonia, nephritis and lymphoma. No body weight or food consumption data were provided. therefore, there are no data to satisfy this requirement.

Oncogenicity studies in two species are required.

83-3 Teratology

A teratology study was submitted but was found to be inadequate to support registration of Tebuthiuron.

Gravid Harlan rats, 25 per group, were offered diets containing 0, 600 1200 or 1800 ppm SE-103 on days 6 - 15 of gestation. However, no detailed analytical data, such as individual dam's body weights or individual litter data, were supplied. In addition, the test material was offered in the diet rather than being given by gavage as recommended. There are therefore no data to satisfy this requirement.

Teratology studies in two mammalian species are required.

83-4 Reproduction

Sufficient data are available to satisfy the requirement for a multi-generation reproduction study.

Harlan rats, 25/sex/dose, were offered diets containing 0, 100, 200 or 400 ppm (5, 10 or 20 mg/kg bwt./day) technical Tebuthiuron through two generations of offspring (MRID 90108). No adverse effects were reported except that F1 females in the pre-mating phase showed a lower rate of body weight gain in the 200 and 400 ppm groups. No adverse effects were reported on reproductive performance at any level.

The NOEL for reproductive effects is > 400 ppm (20 mg/kg bwt./day). The NOEL for systemic effects is 100 ppm (5.0 mg/kg bw./day).

84 Series Mutagenicity

84-2 Mutagenicity Tests

Gene Mutation

1. An Ames plate incorporation assay was performed using bacterial strains of S. Typhimurium LT-2: 946, TA-1535, TA-100, C-3076, TA-1537, D-3042, TA-1538 and TA-98 with and without activation.

2-AA, 2NF, 9-AmAc and MMNG plates served as positive controls. Doses of technical Tebuthiuron used were 5 to 5000 ug/plate (MRID 141691). No test plates showed evidence of induction of point mutations in 8 testor strains of S. Typhimurium.

Technical Tebuthiuron was not mutagenic either with or without metabolic activation.

2. An L5178Y mouse lymphoma assay for the induction of forward mutations using the $TK^{+/-}$ cell line was sensitive to direct acting and activation-dependant mutagens (MRID 145041). Technical Tebuthiuron was slightly mutagenic in the non-activated assays. Mutation indices of 2.0, 2.0 and 2.7 were detected in Technical Tebuthiuron-treated cultures at concentrations of 200, 400 and 500 ug/ml respectively. Technical Tebuthiuron was not mutagenic in activated assays.

   Technical Tebuthiuron is slightly mutagenic in the mouse lymphoma non-activated assay.

The requirement for Gene Mutation assays is satisfied.

Structural Chromosomal Abberation

There are no valid assays available. A structural chromosomal abberation study is required.

Tests for other Genotoxic Effects

There are no valid assays available. Such data are required.

85 Series Special Studies

85-1 Metabolism

Some metabolism data are available to partially fulfill this requirement.

Radio-labeled technical Tebuthiuron was administered in the diet at 100 and 200 ppm (5 and 10 mg/kg bwt./day, respectively) to lactating rats immediatley post-partum (MRID 106081). The period of diet administration was 48 hours. The dams were milked and the amount of activity in the milk was determined. The mean 14C levels in rats' milk was 2.7 ppm and 6.2 ppm for the 100 ppm and 200 ppm rats respectively.

Technical Tebuthiuron and/or its metabolites appears in the milk of lactating rats.

General Metabolism studies are not available for technical Tebuthiuron. Such studies are required.

85-2 Domestic Animal Safety

This study is not needed since domestic animals will not be routinely exposed to technical Tebuthiuron or its formulations.

85-3 Dermal Absorption

A dermal absorption study is not needed because there are no serious toxic effects by the oral or inhalation routes of exposure, and because dermal exposure is not expected to be significant.

Information on Human effects

There is no information on human health effects.

C. Data Gaps

Tebuthiuron is registered for food crop uses and therefore the following Guideline toxicology studies can be required for registration:

81-1 Acute Oral
81-2 Acute Dermal
81-3 Acute Inhalation
81-4 Primary Eye Irritation
81-5 Primary Dermal Irritation
81-6 Dermal Sensitization

82-1 Subchronic Oral in two species
82-2 Subchronic Dermal (21 Day)
82-3 Subchronic Dermal (90 Day)
82-4 Subchronic Inhalation

83-1 Chronic Toxicity
83-2 Oncogenicity studies in two species.

83-3 Teratogenicity studies in two species.

83-4 Reproduction studies

84-2 Mutagenicity Tests

Gene Mutation

Structural Chromosomal Abberation

Tests for other Genotoxic Effects

85-1 General Metabolism

Based on this assessment of the toxicology data base the following Guideline studies are required:

81-1 Acute Oral
81-2 Acute Dermal
81-4 Primary Eye Irritation
81-5 Primary Dermal Irritation
81-6 Dermal Sensitization
83-1 Chronic Toxicity (Rodent)
83-2 Oncogenicity Studies (Two Species)
83-3 Teratogenicity Studies (Two Species)
84-2 Mutagenicity Tests (Chromosomal aberrations and tests for other Genotoxic Effects).

85-1 General Metabolism

This requirement is only partially satisfied. The registrant is required to design and perform Guideline tests that: 1) show the absorption, distribution and excretion of the test material in a mammalian system; 2) identify the major metabolites in a mammalian system.

7. ADI (RfD) Reassessment

Tolerances for residues of Tebuthiuron on food crops have been established under 40 CFR 180.399.

Data available to assess the ADI include: a one year dog feeding study, NOEL = 25.0 mg/kg bwt./day based on increased liver, kidney and thyroid gland ratios and increased alkaline phosphatase, alanine transaminase and thrombocyte count values in high dose males and females; a ninety day rat feeding study NOEL of 50 mg/kg bwt./day based on increased liver, kidney and gonadal ratios in males and females on the high dose, and increased spleen and prostate ratios in high dose males. A multi-generation rat reproduction study NOEL for reproductive effects was was greater than 20 mg/kg bwt./day, the highest level tested. The systemic NOEL in this study was 5.0 mg/kg bwt./day.

Using the most sensitive study, the two generation rat reproduction study (MRID 90108), the Toxicology Branch has tentatively calculated the PADI for Tebuthiuron. From the systemic NOEL of 100 ppm (5.0 mg/kg bw./day) and an uncertainty factor of 1000, we calculate that the Provisional ADI (PADI) for Tebuthiuron is 0.0050 mg/kg bwt./day. The safety factor is based on the absence of a chronic rat study*.

These calculations will be submitted to the RED Work Group for final resolution of the ADI question for Tebuthiuron. Their findings will be appended to this Standard.

E. Toxicological Issues

Tebuthiuron is one of a class of substituted dimethylurea herbicides, others being Diuron and Monuron.

Diuron [3-(3,4-dichlorophenyl)-1,1-dimethylurea], was tested in mice and found to produce a significantly increased incidence of bladder carcinomas in male and female mice fed the material in the diet for two years at a level of 2500 ppm (357 mg/kg bwt./day). Lower doses did not produce the lesions (Raleigh, 1985)1/.

Monuron [3-(p-chlorophenyl)-1,1-dimethylurea] when offered in the diet of F344/ male rats at levels of 750 or 1500 ppm (37.5 mg/kg bwt./day and 75.0 mg/kg bwt./day, respectively) produced increased incidences of renal tubular cell adenomas and carcinomas and increased neoplastic nodules and carcinomas of the liver. Female rats were negative for oncogenic effects of technical Tebuthiuron. B6C3F1 male and female mice did not show neoplasms when receiving diets containing 5,000 or 10,000 ppm (714 and 1428 mg/kg bwt./day, respectively) technical Tebuthiuron (NTP, 1984)2/.

Linuron [N-(-3,4-dichlorophenyl)-N'-methoxy-N'methylurea)], a monomethylurea herbicide, produced testicular hyperplasia and adenomas, and interstitial cell tumors in male mice fed the material in the diet for one year at 125 and 625 ppm (18 and 89.3 mg/kg bwt./day/day, respectively) (Albert, 1984)3 .

These findings strongly suggest that the urogenital tissues in rodents are especially sensitive to substituted methylurea compounds. The liver is also sensitive. In the subchronic rat feeding study of technical Tebuthiuron noted above (MRID 00206[illegible]) there was an increase in the relative kidney and gonadal body weight ratios, indicative of the sensitivity of these tissues to this class of materials.

---

* SCP # 1012, 9/12/85, F. M. Farber, Ph.D.

1/ Raleigh, F. W., DuPont letter to P. Taylor, PM 25, 4/25/85.

2/ NTP-83-111, Bioassay of Monuron in F344/ rats and B6C3F1 mice. NIH Pub. # 84-2522, April, 1984.

3/ Albert, T., et al. CAR Report on Diuron Carcinogenicity.

12

The chronic dog oral ingestion study noted above (MRID 146801) showed no adverse effects on urogenital organs, but there was a mild hepatomegaly associated with increased alanine transaminase and alkaline phosphatase (indicative of hepatotoxicity) at the high dose. No histopathological changes were reported for any organs, however.

Based on these considerations, the Agency will not consider establishing further food tolerances pending receipt of the required chronic and oncogenicity studies. These must specifically address the question of potential oncogenic response in the urogenital system and the liver, with careful attention being given to the histopathology of the kidney, bladder, gonads and associated organs, and the liver.

TABLE A
GENERIC DATA REQUIREMENTS FOR TECHNICAL PESTICIDES

Data Requirement	Composition	1/ Use Patterns	2/ Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
158.135 Toxicology					
ACUTE TESTING:					
81-1 - Acute Oral - Rat	TGAI	ABD	No.		Yes
81-2 - Acute Dermal -	TGAI	ABD	No.		Yes
81-3 - Acute Inhalation - Rat	TGAI	ABD	Yes	MRID 155730	No
81-4 - Eye Irritation - Rabbit	TGAI	ABD	No.		Yes
81-5 - Dermal Irritation - Rabbit	TGAI	ABD	No.		Yes
81-6 - Dermal Sensitization - Guinea Pig	TGAI	ABD	No.		Yes
81-7 - Acute Delayed Neurotoxicity - Hen	TGAI	ABD	No.		No 4/
SUBCHRONIC TESTING:					
82-1 - 90-Day Feeding -					
Rodent	TGAI	ABD	Yes	MRID 20662	No
Non-rodent	TGAI	ABD	No		No 5/

TABLE A
GENERIC DATA REQUIREMENTS FOR TECHNICAL TEBUFENOZIDE

Data Requirement	Composition 1/	Use Pattern 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)?	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
58.135 Toxicology (Cont.)					
82-2 - 21-Day Dermal-	TGAI	ABD	Yes	MRID 258052	No
82-3 - 90-Day Dermal-	TGAI	ABD	No		No 6/
82-4 - 90-Day Inhalation -	TGAI	ABD	No		No 6/
82-5 - 90-Day Neurotoxicity-	TGAI	ABD	No		No 7/
CHRONIC TESTING:					
83-1 - Chronic Toxicity -					
Rodent	TGAI	ABD	No		Yes
Non-rodent	TGAI	ABD	Yes	MRID 146801	No
83-2 - Oncogenicity Study -					
Rat	TGAI	ABD	No		Yes
Mouse	TGAI	ABD	No		Yes
83-3 - Teratogenicity -					
Rat	TGAI	ABD	No		Yes
Rabbit	TGAI	ABD	No		Yes
83-4 - Reproduction -	TGAI	ABD	Yes	MRID 20739; 90103	No

TABLE A
GENERIC DATA REQUIREMENTS FOR TECHNICAL TEBUTHIURON

Data Requirement	1/ Composition	Use 2/ Pattern	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?3/
158.135 Toxicology (continued)					
MUTAGENICITY TESTING					
84-2 - Gene Mutation	TGAI	ABD	Yes	MRID 144041 MRID 141691	No
84-2 - Chromosomal Aberration	TGAI	ABD	No		Yes
84-2 - Other Mechanisms of Mutagenicity	TGAI	ABD	No		Yes
SPECIAL TESTING					
85-1 - General Metabolism	PAI or PAIRA	ABD	Partially	MRID 106081	Yes 8/

1/ Composition: TGAI Technical Grade Active Ingredient; PAI = Pure Active Ingredient; PAIRA = Pure Active Ingredient, Radiolabelled; Choice = Choice of several test substances determined on a case-by-case basis.
2/ The use patterns are coded as follows: A = Terrestrial, Food Crop; B = Terrestrial, Non-Food; C = Aquatic, Food Crop; D = Aquatic, Non-Food; E = Greenhouse, Food Crop; F = Greenhouse, Non-Food; G = Forestry; H = Domestic Outdoor; I = Indoor; IP = Industrial Preservative.
3/ Unless otherwise specified data must be submitted no later than six months after publication of this Standard.
4/ This test is only for compounds which are organophosphate inhibitors of cholinesterase, or related to such inhibitors or are metabolites of such inhibitors. Tebuthiuron is not an organophosphate; therefore, a study is not required
5/ A subchronic oral toxicity study in a non-rodent species is not required because there is a one year dog study available.
6/ This study is not required for the present use pattern.
7/ Since an acute neurotoxicity study is not required, and there is no evidence of neurotoxicity in mammalian species this study is not required.
8/ Data defining the absorption, distribution, metabolites and their excretion patterns must be submitted no later than after publication of this Standard.

TABLE B

PRODUCT SPECIFIC DATA REQUIREMENTS FOR MANUFACTURING-USE PRODUCTS CONTAINING TEBUTHIURON

Data Requirement	Composition 1/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 2/
§158.135 Toxicology A,B,D				
ACUTE TESTING				
81-1 - Acute Oral - Rat	MP	No		Yes
81-2 - Acute Dermal	MP	No		Yes
81-3 - Acute Inhalation - Rat	MP	No		Yes
81-4 - Primary Eye Irritation - Rabbit	MP	No		Yes
81-5 - Primary Dermal Irritation - Rabbit	MP	No		Yes
81-6 - Dermal Sensitization Guinea pig	MP	No		Yes

1/ Composition: MP = Manufacturing-use product.

2/ Unless otherwise specified data must be submitted no later than six months after publication of this Standard

005822

BIBLIOGRAPHY

00020662 Todd, G.C.; Gibson, W.R.; Kiplinger, G.F. (1972) The Toxicological Evaluation of EL-103 in Rats for 3 Months. (Unpublished study received Mar 13, 1973 under 1471-97; submitted by Elanco Products Co., Div. of Eli Lilly and Co., Indianapolis, Ind.; CDL: 006422-G)

00020714 Todd, G.C.; Gibson, W.R.; Hoffman, D.G.; et al. (1976) The Toxicological Evaluation of Tebuthiuron (EL-103) in Rats for Two Years: Toxicology Report # 7. (Unpublished study received Dec 1, 1976 under 1471-EX-43; submitted by Elanco Products Co., Div. of Eli Lilly and Co., Indianapolis, Ind.; CDL:230139-A)

00020717 Todd, G.C.; Gibson, W.R.; Hoffman, D.G.; et al. (1976) The Toxicological Evaluation of Tebuthiuron (EL-103) in Mice for Two Years: Toxicology Report # 8. (Unpublished study received Dec 1, 1976 under 1471-EX-43; submitted by Elanco Products Co., Div. of Eli Lilly and Co., Indianapolis, Ind.; CDL:230139-D)

00020803 Todd, G.C.; Markham, J.K.; Adams, E.R.; et al. (1972) Rat Teratology Study with EL-103. (Unpublished study received Mar 13, 1973 under 1471-97; submitted by Elanco Products Co., Div. of Eli Lilly and Co., Indianapolis, Ind.; CDL:006422-C)

00090108 Hoyt, J.A.; Adams, E.R.; Owen, N.V.; et al. (1981) A Two-generation Reproduction Study with Tebuthiuron (Compound 75503) in the Wistar Rat: Studies R03780 and R08780. (Unpublished study received Dec 10, 1981 under 1471-109; submitted by Elanco Products Co., Div. of Eli Lilly and Co., Indianapolis, Ind.; CDL:246374-A)

00106081 Adams, E.; Magnussen, J.; Emmerson, J.; et al. (1982) Radiocarbon Levels in the Milk of Lactating Rats Given 14C Tebuthiuron (Compound 75503) in the Diet: Study R13781. (Unpublished study received Jul 15, 1982 under 1471-109; submitted by Elanco Products Co., Div. of Eli Lilly and Co., Indianapolis, IN; CDL: 070985-C)

00141691 Rexroat, M. (1984) The Effect of Tebuthiuron (Lilly Compound 75503) on the Induction of Reverse Mutations in Salmonella typhimurium Using the Ames Test: Study 840326AMS655. Unpublished study prepared by Eli Lilly & Co. 28 p.

00145041 Oberly, T. (1984) The Effect of Tebuthiuron (Lilly Compound 75503) on the Induction of Forward Mutation at the Thymidine Kinase Locus of L5178Y Mouse Lymphoma Cells: Studies 840410MLA655; 840606MLA655; 840613MLA655. Unpublished study prepared by Eli Lilly and Co. 40 p.

00146801 Todd, G.; Means, J.; McGrath, J. (1985) The Toxicologic Evaluation of Tebuthiuron (Lilly Compound 75503) Given Orally to Beagle Dogs for One Year: Study D04283. Unpublished study prepared by Lilly Research Laboratories. 348 p.

00149733 Brown, G. (1985) Subchronic (21-Day) Dermal Toxicity Study in New Zealand White Rabbits with Technical Tebuthiuron: Study B01484. Unpublished study prepared by Lilly Research Laboratories. 211 p.

00155730 Markey, T. (1985) The Acute Inhalation Toxicity of Technical Tebuthiuron (EL-103, Compound 75503): Study No. R-H-023-85. Unpublished study prepared by Lilly Research Laboratories. 15 p.

ox Chem No. 366AA - TEBUTHIURON File Last Updated 06/20/86 Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Registration Standard Acute Inhalation - rat; Lilly Res. Labs.; R-11-023-85; 6/85.	EL-103; 98.9%	MRID 155730	LC_{50} > 3.7 mg/L (HGP). No toxic signs reported.	III	005822 Guideline 005629
90-Day feeding - rat; Lilly Res. Lab.; 1972	Technical	MRID 20662	Systemic NOEL = 1,000 ppm Systemic LEL = 2,500 ppm (growth suppression, pancreatic lesions)		000344 000347
21-Day dermal - rabbit; Lilly Research; 130-1434; March 1985	97.8%	258052	NOEL = 1000 mg/kg/ (only dose tested).		Guideline 004748
One year feeding - dog; Lilly Res. Lab.;DO4283; 1/85.	Technical	MRID 146801	Increased liver ratios; increased alkaline phosphatase in high dose animals. Levels offered: 0, 12.5, 25.0 and 50. mg/kg/day. NOEL = 25.0.		Minimum
Two-generation reproduction - rat; Lilly Res. Lab.; R03780 and R08780; 1/31	Tech. 93% pure	MIRD 90108	Systemic Toxicity NOEL $\geq$ 100 ppm Reproductive NOEL > 400 ppm		Guideline 001459 002160
Mutagenic - Ames; Lilly Research Laboratory; 840326AMS655; April 1984	EL-103 98.0% pure Lot # X-35920	MRID 145041	EL-103 with and without metabolic activation did not induce point mutation in S. typhimurium strains - TA98, TA100, TA1535, TA1537, and TA1538.		Acceptable 004434

005822

ox Chem No. 366AA - TEBUTHIURON File Last Updated 06/20/86 Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
[illegible] - Induction of Forward Mutation - Mouse Lymphoma Cells; Lilly Research Laboratories; #840410MLA655, 840606MLA655, and 840612MLA655; August 1984	EL-103 98.0% pure Lot # X-35920	MRID [illegible]	The L5178 TK+/- mouse lymphoma cell assay was sensitive to direct acting and activation-dependent mutagens. Tebuthiuron was mildly mutagenic in the assay without metabolic activation. In the original non-activated assay, mutation indexes of 2.0 and 2.4 were detected in tebuthiuron treated culture at concentrations of 700 and 800 ug/ml, respectively. Mutation indexes of 2.0, 2.0, and 2.7 occurred at tebuthiuron concentrations of 200, 400 and 500 ug/ml, respectively, in a repeat of the non-activated assay. Mutation was not induced by tebuthiuron in the original and repeat assays with metabolic activation.		Acceptable 004434
Milk Residues - rat; Lilly Res. Labs.;R13781; 1/82.	Technical, 98% radio-labeled C14.	MRID 106081	100 and 200 ppm fed immediately post-partum for 2 days. 14C materials appeared in milk at 2.7 and 6.2 ppm respectively.		Acceptable

BEST AVAILABLE COPY

005822

Reviewed by: D. Ritter DR 2-27-87
Section I , Tox. Branch (TS-769C)
Secondary reviewer: R. Bruce Jaeger
Section I , Tox. Branch (TS-769C)

81-3
Rap 05822

DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation, Rat TOX. CHEM. NO. 366AA

ACCESSION NUMBER: 260636 YRID NO.: 155730

TEST MATERIAL: N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea.

SYNONYMS: Tebuthiuron; Lilly Compound # 75503; EL-103.

STUDY NUMBER(S): R-H-023-85.

SPONSOR: Elanco Products Co., Indianapolis, IN.

TESTING FACILITY: Lilly Research Laboratories, Greenfield, IN.

TITLE OF REPORT: The Acute Inhalation Toxicity of Technical Tebuthiuron.

AUTHOR(S): G.C. Todd, T.F. Markey.

REPORT ISSUED: June, 1985.

CONCLUSIONS: The Four Hour LC_{50} in rats was > 3.696 mg/L air.

Classification: CORE - Guideline.

Special Review Criteria (40 CFR 154.7) None.

A. MATERIALS:

1. Test compound: EL-103 Description: _____
Batch #: X-35920 . Purity: 98.9% .

2. Test animals: Species: Rat , Strain: C-F. ,
Age: 62-69 days Weight: _____, Source: Charles River Labs, Inc., Portage, MI.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned 10 M & 10 F to a single test group to be exposed to a nominal concentration of 13.13 mg/L air (Total gravimetric = 3.90 mg/l and an analytical concentration of 3.396 mg/L air).

Husbandry - Standard GLP.

Feed and Water - ad libitum following exposure.

Body Weights - initially and on days 1, 3, 5, 7 and 14.

Observations for mortality and signs of toxicity - immediately after exposure, twice daily during week one, then daily on weekends for two weeks.

Particle size was determined using a Sierra Ambient Cascade Impactor with fiberglass collectors.

2. Compound Administration:

Animals were fitted to "nose only" exposure devices that were adjusted to receive the test material in an airflow of 15 L/min. The aerosol was generated using a Wright Dust mechanism calibrated to deliver the test material at a nominal concentration of 13.13 mg/L air. Duration of exposure was 4 hours.

C. RESULTS:

Feed, water and body weights - no deleterious effects reported.

Mortality - No animals died during the test or observation periods.

Observations - No signs of toxicity were reported.

Particle size was determined to 3.73 microns calculated as the mass median equivalent aerodynamic diameter.

Actual exposure to EL-103 was calculated to be 3.696 mg/L air.

D. CONCLUSIONS:

The LC_{50} for inhalation exposure in this rat study is > than 3.696 mg/L air.

Toxicity Category: III.

OPPT Rating: Guideline.

DQR 2-27-87

82-1
Rat 005822

Reviewed by: D. Ritter
Section 1 , Tox. Branch (TS-769C)
Secondary reviewer: R. Bruce Jaeger
Section , Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Subchronic Feeding, Rat TOX. CHEM. NO. 366AA

ACCESSION NUMBER: NA MRID NO.: 20662

TEST MATERIAL: N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea.

SYNONYMS: Tebuthiuron; Lilly Compound # 75503; EL-103.

STUDY NUMBER(S): R-491

SPONSOR: Eli Lilly and Company, Greenfield, IN.

TESTING FACILITY: Lilly Research Laboratories, Greenfield, IN.

TITLE OF REPORT: The Toxicological Evaluation of EL-103 in Rats for 3 Months.

AUTHOR(S): Todd, G.C., W. R. Gibson & G. F. Kiplinger.

REPORT ISSUED: September, 1972.

CONCLUSIONS: The NOEL is 1000 ppm (50 mg/kg bwt./day) in the diet based on increased relative liver, kidney, prostate, spleen and gonad weights in high dose males and females. There was also slight vacuolization of pancreatic acinar cells in high dose males and females.

Classification: CORE- Minimum data.

Special Review Criteria (40 CFR 154.7) None identified.

A. MATERIALS and METHODS:

See the review of Reg. # 1471-491, D. Ritter, 2 21/75 (copy attached).

Harlan rats were offered diets containing 0, 400, 1000 or 2500 ppm for three months. Blood samples were obtained at termination and analysed. Histopathological examination was done on representative tissues.

B: RESULTS AND CONCLUSIONS:

High dose males and females showed reduced body weights, and increased relative liver, kidney and gonads; males in addition showed increased relative spleen and prostate gland weights. There was slight vacuolization of the pancreatic acinar cells in the high dose males and females.

2. Subacute Toxicity Data

(Submitted in support of registration # 1471-97, Spike *80W).

A. 3 Month rat Feeding Study (#R-491)

Methods:

Harlan rats (28 - 35 Gm) were randomized into four groups of 10 male and 10 females each and were offered diets containing 0, 400, 1000 or 2500 ppm EL-103 for three months. Animals were monitored for appearance, behavior, food intake, body weights, food efficiency utilization and mortality. Eye were examined initially and at termination. Blood samples were obrained terminally and Hct., Hb., RBC's, total and differential leukocytes, prothrombin times; BUN, Glucose, SGPT were determined.

Histopathological examination was performed on the following tissues and organs: (*) weights obtained

liver*	heart*
kidney*	spleen*
thyroid*	adrenals*
gonads*	prostate*
uterus*	large gut
small gut	lungs
lymph node	mammary gl.
pancreas	salivary gl.
stomach	muscle
thymus	urinary bladder

Results:

High dose males and females demonstrated decreased body weights; increased liver, kidney and gonad weight ratios; males showed in addition increased ratios for spleen and prostate gland. There was a suggestion of thyroid hypertrophy in the middle dose males and females, but not in the high dose-animals.

Clinical chemistry findings were not altered at any level by treatment.

Adverse histopathological findings were confined to the appearance of a vacuolization of the acinar cells of the pancreas at the 2500 ppm level.

Conclusions:

The 90 day rat feeding NEL is 1000 ppm EL-103 based on systemic effects of altered organ/body weight ratios and the appearance of adverse histopathology of the pancreas in high dose animals.

B: Dog 90 day feeding study (D-398-71)

Methods:

Pure-bred Beagle dogs were divided into four groups of two females and two males each and were offered diets containing 0, 500, 1000 or 2500 ppm EL-103 for 3 months (90 days). The animals were observed for appearance, behavior, food consumption and body weight initially and at suitable intervals thereafter. Ophthalmoscopic examination of the eyes was done initially and a termination. Blood samples were obtained initially and at 1, 2 and 4 weeks and at monthly intervals thereafter. These were examined for calcium, inorganic phosphorus, glucose, BUN, Cholesterol, total protein, albumin, total bilirubin, Alk. Ph., LDH, and SGOT. In addition, Hb., Gct., RBC's total and differential leukocytes, reticulocytes, clotting time, platelets, sed rate and prothrombin times were determined.

Gross and microscopic histopathology was performed and the following organs and tissues were examined: (*)= weights obtained.

liver*	kidney*
heart*	spleen*
gonads*	adrenals*
thyroid*	brain
marrow	large and small gut
gall bladder	lungs
lymph nodes	mammary gl.
pancreas	putuitary
salivary gl.	stomach
muscle	thymus
bladder	prostate/uterus

Urine samples were obtained and examined for sugar, pH, protein, blood and Sp. Gr.

Results:

Anorexia was noted especially in the high-dose animals, leading to some weight loss. There was no mortality. Behavior, and appearance were unremarkable at all test levels. No abnormalities were seen in the hematological or urinalyses studies.

Clinical chemistry findings indicated increased BUN in the 2000 ppm females; in addition, this group exhibited increasing levels for Alkaline phosphatase, up to four-fold over that of controls. Levels of this parameter had returned to normal at the terminal sampling. The 2000 ppm males likewise demonstrated this finding. There were no urinary abnormalities.

1000 ppm females and males demonstrated increased thyroid/body weight ratios and the 2000 ppm females also showed increased spleen ratio.

Histopathological findings were negative for adverse effect of EL-103.

Conclusions:

The systemic NEL for feeding of EL-103 to dogs for three months is considered to be 500 ppm on the basis of increased thyroid ratios, increased Alkaline phosphatase values and increased BUN in test animals.

C. Rat Teratology Study (R-632)

Methods:

Pregnant Harlan rats were offered diets containing 0, 600, 1200 or 1800 ppm EL-103 during gestation days 6-15. Pups were obtained by Ceasarian section and were examined for weight, sex distribution, external visceral and skeletal anomalies. Uteri and ovaries were examined for corpora lutea, distribution of fetuses, resorptions and litter size.

Approximately a third of the fetuses in each litter were fixed in buoin's solution for visceral examination and the remainder were cleared for skeletal examination.

Results:

Abnormalities of somatic architechture were few in number and low in severity and were not dose related. Body weights and other paramaters were not adversely affected.

Conclusions:

EL-103 is not a teratogen in rats at up to 1800 ppm when given in the diet during days 6-15 of gestation.

Reviewer: David C. Rutter /s/ David C. Rutter 2-21-75

2nd Reviewer George E. Ahtman, DVM /s/ G E O 2-21-75

12-27-87

82-2 005822

Rabbit

Reviewed by: D. Ritter.
Section I , Tox. Branch (TS-769C)
Secondary reviewer: R. Bruce Jaeger. 12/27/87
Section I , Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: 21 Day Dermal, Rabbit TOX. CHEM. NO. 366AA

ACCESSION NUMBER: 258052 MRID NO.: 149733

TEST MATERIAL: N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea.

SYNONYMS: Tebuthiuron; Lilly Compound # 75503; EL-103.

STUDY NUMBER(S): 801484

SPONSOR: Elanco, Products, Indianapolis, IN.

TESTING FACILITY: Lilly Research Laboratories, Greenfield, IN.

TITLE OF REPORT: Subchronic (21 day) Dermal Toxicity Study in New Zealand White Rabbits with Technical Tebuthiuron (EL-103, 75503).

AUTHOR(S): G. Brown.

REPORT ISSUED: March, 1985.

CONCLUSIONS: NOEL ≥ 1000 mg/kg bwt.

Classification: CORE - Guideline

Special Review Criteria (40 CFR 154.7) None exceeded.

PROCEDURES:

See the R. Landolt review of EPA # 1471-147 & 101, 10/30/85 and the D. Ritter review of 12/12/86.

Two groups of five male and five female albino rabbits were dermally exposed to 0 or 1000 mg/kg bwt of technical Tebuthiuron, 6 hours per day for 21 days. Shaved area of exposure was about 10 % of the total body surface area.

RESULTS:

No signs of toxicity or mortality were reported. 2/10 animals showed slight erythema that cleared by day 7.

005822

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

005625

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCE

DEC 12 1986

TO: Mr. R. Taylor, PM # 25
Herbicides/Fungicides Branch
Registration Division TS-767C

THRU: R. Jaeger, Section Head
Rev. Sec. # 1/Toxicology Branch
Hazard Evaluation Division TS-769C

FROM: D. Ritter, Toxicologist
Rev. Sec. # 1/Toxicology Branch
Hazard Evaluation Division TS-769C

Subject: EPA # 1471/147 and 101 - Tebuthiuron, Company response to reject letter of 11/18/85. 21 Day Rabbit Dermal Toxicity Assay.

Registrant: Elanco, Greenfield, IN.

Caswell #: 366AA.

Elanco responds to certain findings cited in the 10-30-85 TOX review of a 21 Day Dermal study (# Bu1484, dated March, 1985, Acc. # 258052, Ray Lancolt). The study was classified as CORE Supplementary because the single treatment level did not constitute a NOEL. The findings, the Company responses and our evaluations are as follows:

TOX review finding:

A NOEL is less than 1000 mg/kg based on the following considerations:

1. Decreased body weight gain and food consumption were observed for one animal.

Company response:

1. Such effects are common among animals during the first week of treatment. The animal subsequently gained weight. No histopathological effects or obvious clinical signs were present. The effects were isolated, and were not related to treatment.

Our Evaluation:

1. We agree with the Sponsor. That the effects occured in only one animal out of five treated supports his contention that they could not be firmly attributed to exposure to tebuthiuron.

TOX review finding:

2a. Significant increases in treated male blood glucose levels.

2b. Decrease in bilirubin and alkaline phosphatase values in treated males.

Company response:

2a. Blood glucose levels in the Sponsor's rabbit colony show a wide variation depending on the time feed was last ingested and on the individual animals' response to handling. The treated male animal blood glucose values were only 10.9% higher than the controls' values at termination but were 10.5% less than the initial values and were well within historical normal limits.

2b. Values for treated male bilirubin and alkaline phosphatase were also within normal limits for these parameters. Since there were no supporting histopathological alterations the findings are not of toxicological significance.

Our Evaluation:

2a. We agree with the Sponsor as to glucose. This parameter is highly variable even in normal subjects and can be influenced by such things as physical stress(1). Moreover, the fairly small increase (10.9%) over control values can reasonably be considered to be within normal limits.

2b. The reduced values reported for bilirubin and alkaline phosphatase in treated animals in this study were not statistically significantly different when compared to the controls.

---

(1) Tietz, N. W. Chemical Guide to Laboratory Tests. Saunders. 1983. pp. 230-232.

30

TOX review finding:

3. Decreased female relative adrenal weights were reported.

Company Response:

3. The decreases were slight and not statistically different from those of the controls.

Our Evaluation:

3. The decreases were not statistically significant; hence the apparent effect is not toxicologically meaningful.

TOX review finding:

4. Increased absolute and relative spleen weights were reported for the treated females and males.

Company Response:

4. These values for the treated animals were within the normal range of variability in the Sponsor's colony. Moreover, the differences were not statistically significant.

Our Evaluation:

4. We agree with the Sponsor. The differences in relative and absolute spleen weights in the treated females were small and were not statistically significant when analysed using Student's "t" test.

TOX review finding:

5. One treated female showed a congested liver.

Company Response:

5. The finding was not supported by histopathological or clinical chemistry/hematology findings. The occurence in one female is considered to be isolated and not related to exposure to tebuthiuron.

Our Evaluation:

5. We agree with the Sponsor. An isolated occurence of a finding cannot of itself be considered a treatment-related effect.

Overall Conclusions:

We agree with all the Sponsor's responses. The effects noted were in no instance indicative of demonstrated toxicological response.

Accordingly, we conclude that the study should be reclassified as CORE Guideline, and that it therefore fulfills the requirement for the 21 day Dermal Toxicity assay under 40 CFR §158.135 (82-2).

CASWELL FILE
005822

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OCT 30 1985

004743

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBEJECT: Tebuthiuron
N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-
N,N'-dimethylurea
Tox. Chem. 366AA

FROM: Ray Landolt
Review Section #1
Toxicology Branch/HED (TS-769)

TO: Robert J. Taylor
Registration Division (TS-767)

THRU: Robert B. Jaeger, Section Head
Review Section #1
Toxicology Branch/HED (TS-769)

Registrant: Elanco Products Co. May 9, 1985

EPA No. 1471-147 (dry flowable preemergence and postemergence herbicide)
1471-101 (Technical)

Action Requested:

1. Review of a 21-Day dermal toxicity study conducted with the technical formulation (97.8%) identified as EL-103, compound 75503.

2. Request for an exemption from a 21-day dermal toxicity testing for the 85% dry flowable formulation based on "no systemic toxicity at the limit dose (1000 mg/kg) in a 21-day dermal toxicity study", conducted with the technical formulation.

Recommendation:

The 21 day dermal toxicity study on the technical formulation could be upgraded with additional dosage levels to establish a systemic no-effect level rather than conduct a 21-day dermal study on the 85% use formulation.

21-Day Dermal - Rabbit
Lilly Research Lab. No.. B01484, March 1985, Acc. No. 258052

A. Procedure

Two groups of five male and five female 12-16 week old New Zealand White rabbits weighing approximately 2.58 kg were dosed dermally at 0 and 1000 mg/kg, 6 hours per day for 21 consecutive days with the dry form of the technical material (97.8%). The test material was applied to a damp gauze pad that was equivalent in size to 10 percent of each rabbit's body surface area then place on the rabbit's back, covered with an elastic nonocclusive bandage and secured with tape. The animals were fitted with collars and housed individually. Following the 6-hour exposure the dressing was removed and the test areas was rinsed with tap water and dried. Body weights were recorded each week with doses adjusted to changes in body weight. Food consumption was measured daily. Ophthalmic examination, hematology, and clinical chemistry evaluations. were performed initially and at the termination of the study. The animals were observed twice daily for signs of toxicity and for dermal irritation prior to treatment. At the termination of the study all animals were necropsied, organ weights recorded, and tissues collected at necropsy examined microscopically.

B. Results

1. Gross Observations
   a. No signs of toxicity, ocular effects or deaths were reported.

   b. Slight erythema was observed within three days (2/10), clearing by day 7.

   c. The mean body weight gain and food consumption of the test and control groups were comparable. One female (No. 175731) of the treated group failed to gain weight over the test period which was evident by the decrease in food consumption for this animal.

2. Clinical Observations

a. Hematology

i. A statistically significant increase in the mean corpuscular hemoglobin was observed for the treated females, but comparable to the pretest values.

b. Chemistry

i. A statistically significant increase in male glucose values was reported as compared to controls accompanied by an observed decrease in male total bilirubin (22%) and alkaline phosphatase values (22%).

ii. Male alanine transaminase values were statistically decreased as compared to the controls, but comparable to the pretest control values.

3. Terminal Observations

a. Organ weights

i. Increases in ab solute (14-20%) and relative (16-17%) weights of the spleen were observed for both sexes.

ii. Decrease in female relative adrenal (24%) weights were observed.

b. No gross pathological changes were observed.

c. Histopathology

i. Liver congestion was reported for one female (No. 175841) of the treated group.

ii. Focal granulomas of the cerebrum and cerebellum were reported for another female (No. 175831) of the treated group that was "probably due to an infectious organism". The incidence of focal granuloma in the central neverous system of rabbits is a common occurrence (Dr. Kasza).

C. Conculsion

1. Classification of data - Supplementary

2. No observable effect level is less than 1000 mg/kg.
   a. Decreased body weight gain and food consumption were observed for one animal.

   b. Significant increases in male blood glucose levels accompanied by a decrease in bilirubin and alkaline phosphatase values were observed.

   c. Decreased female relative adrenal weights were observed.

   d. Increased absolute and relative spleen weights of both sexes were observed.

   e. Liver congestion was observed for one treated female.

Reviewer's Note: Guidelines recommend that if toxic effects are noted in a single dose study, a full study using three doses may be necessary

TS-769:LANDOLT:sll:X73710:9/25/85 Card 8

DER 2-27-87

83-005822

Dog

Reviewed by: D. Ritter, Toxicologist
Section I, Tox. Branch (TS-769C)
Secondary reviewer: R. Bruce Jaeger, Section Head 3/3/87
Section I, Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: One Year Dog Feeding Study. TOX. CHEM. NO. 366AA

ACCESSION NUMBER: NA MRID NO.: 146801

TEST MATERIAL: N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea.

SYNONYMS: Tebuthiuron; Lilly Compound # 75503; EL-103.

STUDY NUMBER(S): D04283

SPONSOR: Eli Lilly and Company, Greenfield, IN.

TESTING FACILITY: Lilly Research Laboratories, Greenfield, IN.

TITLE OF REPORT: The Toxicological Evaluation of Tebuthiuron (Lilly Compound 75503) to Beagle Dogs for One Year.

AUTHOR(S): Todd, G.; Means, J.; McGrath, J.

REPORT ISSUED: February 1985.

CONCLUSIONS: NOEL = 25.0 mg/kg bwt./day

Classification: CORE-Minimum data.

Special Review Criteria (40 CFR 154.7) None.

A. MATERIALS:

1. Test compound: Tebuthiuron Description: Powder
Batch #: X-35920. Purity: 98.9%.

2. Test animals: Species: Dog, Strain: Beagle,
Age: 5 - 6 mos. Weight: 6 -7 kg., Source: Marshall R. I..

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned 4 M & 4 F to the following test groups:

Control	0.0	mg/kg
Low Dose	12.5	mg/kg
Mid Dose	25.0	mg/kg
High Dose	50.0	mg/kg

37

2. Compound Administration:

   Test Material was administered orally by capsule, once daily, except for Christmas day.

3. Quality assurance procedures were Standard GLP.

4. Animals were weighed on day 3, then weekly thereafter for one year, except for the week of Christmas.

5. Animals received 300 gm feed daily. Water was available ad libitum.

6. Food consumption was estimated daily.

7. Animals were inspected daily for signs of toxicity and mortality.

8. Animals were given a complete physical exam initially and at termination.

9. Opthalmalogical examinations were performed initially, at six months and at termination.

10. Blood was collected initally and at 1, 3, 6 and 12 months for hematological and clinical chemistry analyses from all animals.

    The CHECKED (X) parameters were examined:

    a. Hematology

X	Hematocrit (PCV)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB conc.(MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)
X	Platelet count*	X	Reticulocyte count

Blood Clotting Measurements

X	(Thromboplastin time)
X	Thrombocyte count

* Recommended for chronic studies in accordance with Subpart F guidelines.

b. Clinical Chemistry

	Electrolytes:		Other:
	Calcium*		Albumin*
	Chloride*	X	Blood creatinine*
	Phosphorous*	X	Blood urea nitrogen*
	Potassium*		Cholesterol*
	Sodium*	X	Glucose*
		X	Total Bilirubin*
			Total Serum Protein*

	Enzymes
X	Alkaline phosphatase
	Creatinine phosphokinase*
X	Serum alanine aminotransferase (also SGPT)*
	Serum aspartate aminotransferase (also SGOT)*

* Recommended for chronic studies in accordance with Subpart F Guidelines.

12. Urinalysis

Urine was collected from fasted animals initially and at 1, 3, 6, and 12 months.

The CHECKED (X) parameters were examined.

X	Appearance*	X	Glucose*
	Volume*		Ketones*
X	Specific gravity*		Bilirubin*
X	pH	X	Blood*
X	Sediment (microscopic)*	X	Protein*

* Recommended for chronic studies in accordance with Subpart F Guidelines.

13. Necropsy and Pathology

All animals that died or that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected and prepared for histological examination. The (XX) organs were weighed.

	Digestive system		Cardiovasc./Hemat.		Neurologic system	
X	Salivary glands*		Aorta*	X	Brain*† (cerebrum, cerebellum, brn stm.	
	Esophagus*	XX	Heart*	X	Periph. nerve*	
X	Stomach*	X	Bone marrow*		Spinal cord (3 levels)*	
X	Duodenum*	X	Lymph nodes*	X	Pituitary*	
X	Jejunum*	X	Spleen*	X	Eyes *	
X	Ileum*	X	Thymus*		Glandular	
	Cecum*		Urogenital	XX	Adrenals*	
X	Colon*	XX	Kidneys*††	X	Mammary gland*	
	Rectum*	X	Urinary bladder*	X	Parathyroids*††	
X	Liver*††	XX	Testes*††	XX	Thyroids*††	

* Recommended for chronic studies in accordance with Subpart F Guidelines.
†† Organ weight recommended for chronic non-rodent studies in accordance with Subpart F Guidelines.

X	Gall bladder*	X	Prostate	Other	
X	Pancreas*	XX	Ovaries*††	X	Bone*
Respiratory		X	Uterus*	X	Skeletal muscle*
	Trachea*			X	Skin*
X	Lung*				All gross lesions and masses*

* Recommended for chronic studies in accordance with Subpart F Guidelines.
†† Organ weight recommended for chronic non-rodent studies in accordance with Subpart F Guidelines.

11. Statistics - The following procedures were utilized by Petitioner in analyzing the data: Dunnett and Bartlett.

In addition, Student's "t" test was used by the reviewer when considered appropriate.

C. RESULTS:

1. Mortality and Signs of Toxicity -

All animals survived the experiment to termination. Sings of toxicity were confined to the High dose males & females and consisted of anorexia, emmesis and diarrhea.

The NOEL for these effects is 25.0 mg/kg bwt./day.

2. Body Weights and Feed Consumption -

Low dose male and female body weights were significantly reduced during the study when compared to that of the controls. However, the initial body weights for these animals were also reduced and this effect is not considered to be treatment related. The rate-of-weight-gain was similar for treated and control groups. Feed consumption was not affected by exposure to Tebuthiuron.

The NOEL for these parameters is > 50.0 mg/kg bwt./day.

3. Ophthalmic examination was negative for effect of exposure to Tebuthiuron.

The NOEL for this effect is > 50.0 mg/kg bwt.

4. Blood examination -

- Hematogram

No statistically significant differences were reported except: Thrombocyte counts were increased throughout the study and were significantly increased from 6 months to 12 months in the the High dose males. The NOEL for this parameter is 25.0 mg/kg bwt.

° Serogram

The following blood parameters recommended for chronic studies were not supplied:

Calcium, Albumin, Chloride, Phosphorous, Cholesterol, Potassium, Sodium, Serum aspartate aminotransferase (SGOT), Creatinine phosphokinase, Total Serum Protein and Cholesterol.

Males -

Alanine transaminase was significantly increased at 26, 91 and 363 days in the High dose group. Alkaline phosphatase was significantly increased in the High dose group on day 363. Bilirubin was significantly decreased in the Low dose group but significantly increased in the Middle dose and High dose groups on day 91. It was significantly increased in the Middle dose and High dose groups on day 180 and significantly decreased in all test groups on day 363*.

Females -

Alanine transaminase was significantly increased in the High dose group on day 363. Bilirubin was significantly reduced at all levels on days days 26 and 363. This parameter was significantly increased in the Mid and High dose levels on day 180. The Low dose group was significantly decreased on day 91*. Creatinine values were significantly increased in the Low and High dose groups on day 91, in the Mid and High dose groups on day 180, and in the Mid dose group on day 363*.

Overall, we conclude that the NOEL for serum effects is 25.0 mg/kg bwt, based on the increased alanine transaminase and alkaline phosphatase values in the High dose males, and on increased alanine transaminase in the High dose females.

5. Urinalysis showed no effects that could be related to treatment with tebuthiuron.

The NOEL for this examination is 50.0 mg/kg bwt.

6. Post-Mortem examination -

Gross -

No gross abnormalities were reported. Liver-to-body weight ratios were significantly increased in High dose males and females; Kidney-to-body weight ratios were significantly increased in high dose females. Thyroid gland-to-body weight ratios were significantly increased in the high dose males°.

The NOEL for relative organ weight ratios is 25.0 mg/kg bwt.

---

* The findings for Bilirubin in both males and females, and those for creatinine in the females, were not consistent, being reduced at one observation period and increased at others, and showing no dose relationship over time; we therefore consider that these represent normal biological variation not related to exposure to Tebuthiuron.

° When compared with the corresponding control males using Student's "t" test,

Microscopic -

The following tissues recommended for chronic studies were not examined histologically: Esophagus, Trachea, Lesions & masses, Spinal cord (3 levels) and Aorta.

No histopathological effects were reported for any level tested.

The NOEL for histopathological effects is 50.0 mg/kg bwt.

D. DISCUSSION AND CONCLUSIONS:

The effects produced by oral exposure to Tebuthiuron in this one year dog study included increased relative liver weights in high dose males and females; increased relative kidney weights in high dose females, and increased relative thyroid weights in high dose males. There were no adverse histopathological findings for these organs, however. Alanine transaminase and alkaline phosphatase values were significantly increased in the high dose males, and alanine transaminase in the high dose females, and these increases were substantial, being several times greater than those for the corresponding control groups at termination (day 363). This indicates a significant hepatotoxic effect at this level in both sexes. Increased thrombocyte counts in the High dose males throughout the study appear to be an isolated finding.

The overall NOEL based on relatve organ weight ratios, increased serum alanine transaminase, alkaline phosphatase and increased thrombocyte counts is 25.0 mg/kg bwt./day.

E. CORE CLASSIFICATION:

Minimun data: Recommended serum electrolytes, enzymes and histopathologic examination of recommended tissues were not supplied*.

* Although these parameters are missing, the available data in this study shows there were no startling clinical findings in the other parameters, in the histopathological examinations or in the organ weight ratios. It is therefore doubtful that repeating the study would have any effect on the current NOEL, and would not be likely to identify additional target organs.

Reviewed by: D. Ritter, Toxicologist
Section I, Tox. Branch (TS-769C)
Secondary Reviewer: R. Bruce Jaeger, Section Head
Section I, Tox. Branch

DAR 3-13-87

3/13/87

83-1/2
RAT
005822

DATA EVALUATION REPORT

STUDY TYPE: Chronic/Oncogenicity Study, Rat. TOX. CHEM. NO. 366AA

ACCESSION NUMBER: MRID NO.: 20714

TEST MATERIAL: N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea.

SYNONYMS: Tebuthiuron; Lilly Compound # 75503; EL-103.

STUDY NUMBER(S): R-603 and R-613 (replicate studies)

SPONSOR: Eli Lilly and Company, Greenfield, IN.

TESTING FACILITY: Lilly Research Laboratories, Greenfield, IN.

TITLE OF REPORT: The Toxicological Evaluation of Tebuthiuron (EL-103) in Rats For Two Years.

AUTHOR(S): G. C. Todd, W. R. Gibson, et al.

REPORT ISSUED: November 1976.

CONCLUSIONS: None. Supplemental study. Classification: CORE - Supplementary

Special Review Criteria (40 CFR 154.7) None.

A. MATERIALS, METHODS AND RESULTS:

See the 5/31/77 review by M. Quaife, copy attached, which describes reporting deficiencies in the histopatological evaluations. The deficiencies were reiterated in Dr. Quaife's review of 8/18/78, copy attached. They seem to have been resolved in her 4/24/79 review, copy attached; however, there is no further documentation as to the basis for this apparent resolution, i.e., additional data, etc. Accordingly the deficiencies remain. They include:

1. Only major lesions were reported - not minor and possibly significant ones.

2. Numerous instances of emaciated animals, animals with nephritis and/or lymphoma and pneumonia across all groups. Furthermore, the number of animals dying on test, cannibalized, missing or autolyzed is indicative of unthifty animals or poor GLP.

3. No feed consumption figures were provided.

4. No body weight data (except for a growth graph) except on two year survivors. None on other animals.

5. Details of statistical analyses were not provided, only that "linear trend analysis" and "Z" statistics were performed. Neither were further characterized.

6. No indication of how many rats per sex per group were examined histopathologically for each specific tissue; obviously, not all animals could be examined if missing or autolyzed.

7. Survival at 24 months was inadequate (should be 25% in all groups).

	Study # R-603		Study # R-613		Combined	
	Males	Females	Males	Females	Males	Females
Controls	13/60*	15/60	20/60	15/60	33/120	30/120
0.04 %	9/40*	9/40*	5/40*	11/40	14/80	20/80
0.08 %	11/40	9/40*	9/40*	11/40	10/80	20/80
0.16 %	11/40	12/40	9/40*	15/40	20/80	27/80

* 25% or less survival to termination (minimum of 25% in all groups recommended at 24 months, and 50% at 18 months.

Overall, these deficiencies are borderline between Supplemental and Invalid. It is not possible to upgrade this rating.

Reviewed by: D. Ritter, Toxicologist DR 3-13-87
Section I , Tox. Branch (TS-769C)
Secondary reviewer: R. Bruce Jaeger, Section Head
Section I, Toxicologu Branch
RBJ 3/13/87

83-1 005922
0058.2
mouse

DATA EVALUATION REPORT

STUDY TYPE: Oncogenicity Study, Mouse TOX. CHEM. NO. 366AA

ACCESSION NUMBER: MRID NO.: 20717

TEST MATERIAL: N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea.

SYNONYMS: Tebuthiuron; Lilly Compound # 75503; EL-103.

STUDY NUMBER(S): M-9153 and M-9163 (replicate studies)

SPONSOR: Eli Lilly and Company, Greenfield, IN.

TESTING FACILITY: Lilly Research Laboratories, Greenfield, IN.

TITLE OF REPORT: The Toxicological Evaluation of Tebuthiuron (EL-103) in Mice For Two Years.

AUTHOR(S): G. C. Todd, W. R. Gibson, et al.

REPORT ISSUED: November 1976.

CONCLUSIONS: None. Invalid study. Classification: CORE - Invalid.

Special Review Criteria (40 CFR 154.7) None.

A. MATERIALS, METHODS AND RESULTS:

See the 5/31/77 review by M. Ouaife, copy attached, which describes reporting deficiencies in the histopatological evaluations. The deficiencies were reiterated in Dr. Ouaife's review of 8/18/78, copy attached. They seem to have been resolved until her 4/24/79 review, copy attached; however, there is no further documentation as to the basis for this apparent resolution, i.e., additional data, etc. Accordingly the deficiencies remain. They include:

1. Necropsy reports of early death animals and 2 year termination animals are mixed together with no indication of how many animals per group were sectioned for each tissue; i,e., 10/60, 30/60 or 1/60?

2. Necropsies were not performed promptly on moribund or dying animals as indicated by the numbers of autolyzed, missing and cannibalized animals.

3. An exceptionally high incidence of nephritis, pneumonia, and malignant lymphoma in all groups, and in virtually every animal demonstrates an unthrify rodent colony, making it virtually impossible to detect compound-related effects from the few remaining animals.

4. Clinical chemistry and hematology was performed only at termination and only on the surviving animals.

5. Survival at 18 months was inadequate.

	Study # M-9153		Study # M-9163		Combined	
	Males	Females	Males	Females	Males	Females
Controls	13/60*	12/60*	16/60	15/60*	29/120*	31/120
0.04 %	14/40	8/40*	9/40*	7/40*	23/80	14/80*
0.08 %	7/40*	9/40*	13/40	8/40*	20/80	17/80*
0.16 %	12/40	10/40	13/40	15/40	24/80	25/80

* 25% or less survival to termination (minimum of 25% in all groups recommended for mice at 18 months; 50% at 15 months).

6. Control groups may have been exposed to another compound for three months during the study.

The use of unthrifty animals and the inadvertent exposure of the control groups to another chemical render this study Invalid for CORE purposes. There is no possibility that it could be upgraded by submission of additional data.

Tebuthiuron belongs to the class of substituted urea compounds. It also belongs to a class of compounds which contain a 1,3,4-thiadiazole moiety.

Other PP's: 6G1667 and 5G1562. FAP 5H5066

The formulation, Spike® 20P, consists of pellets of 21.05% tebuthiuron (95%) and [redacted]

Proposed use of the pellets is on rangeland and grass pastures in Texas and Oklahoma to control various undesirable woody plants. Formulation is to be applied at 0.5 to 5 lbs active ingredient/acre at "any time." There are no label restrictions on grazing of livestock.

TOXICOLOGY:

Old TOX data are reviewed by Mr. B. Jaeger, 11/7/74 (1471-EXP-X), and by Mr. D. Ritter, 2/21/75, PP No. 5G1562. They include acute oral (Rat LD_{50} = ca. 600 mg/kg), dermal, and inhalation toxicity, and eye irritation; 90-day rat and dog feeding; and rat teratology; and rat, dog, and rabbit metabolism studies.

New TOX data include rat reproduction; rabbit teratologic; metabolism (in mouse, rat, rabbit, dog, duck, and fish); cattle safety; and 2-year rat and mouse feeding studies. A sensitization study, previously submitted, and the other new TOX studies are abstracted below:

2-year rat feeding studies (R-603 and R-613), G. C. Todd et al., Tox. Div., Lilly Research Labs., Nov., 1976, Sec. C, Book 2, this PP.

Method. In two studies of identical design, groups of 40M and 40F Harlan rats (Wistar-derived), 28-35 days old and 113-216 g in wt, each received 400, 800, or 1,600 ppm tech. (97%) tebuthiuron in the diet (Lilly mill ration) for 2 yrs; there were 60M and 60F controls. Rats were individually caged and given food and water ad lib. The tebuthiuron was from Lots No. 6SG43 and B30-23-149.

Diets were assayed at intervals for content of test chemical - at 0, 6, and 18 months, both at time of preparation and after being aged for one week.

Animals were checked twice daily and, closely, once a week. They were weighed and amount of food consumed determined, weekly.

At 6, 12, and 18 months, 5M and 5F rats/group and, at 24 mos., all survivors were tested for hematocrit, hemoglobin, RBC's and WBC's (total and differential). At 2 yrs, prothrombin time of half of the rats and blood chemical values of the other half were determined.

Reviewed by: Mary L. Quaife, PHD /S/ Mary L Quaife PhD 5-31-77

At 6, 12, and 18 months, blood urea nitrogen, serum glutamic-pyruvic transaminase, and glucose were measured. At 2 yrs, same plus creatinine, total bilirubin, and alkaline phosphatase were determined. A 6 and 18 months, urinalysis (for sp. gr., sugar, pH, protein, and occult blood) was made on 5M and 5F rats/group.

All survivors and animals which died (if not autolyzed) were examined grossly and microscopically for lesions and tumors. Tissues processed for microscopic examination are: Gross lesions; nodules, tumors; skin, mammary gland, salivary gland, lung (with nodules), heart,* thyroid (with parathyroid),* stomach, duodenum, jejunum, ileum, colon, mesenteric lymph node, liver (with nodules),* skeletal muscle, thymus, pancreas, spleen,* kidney,* adrenal,* urinary bladder, prostate,* testis,* ovary,* uterus,* brain, pituitary, eye, spinal cord, and sciatic nerve. Organs starred were weighed. Formalin-fixed tissues were stained with hematoxylin and eosin.

We note, the experimenters arrogated to themselves the determination as to which microscopic findings are significant enough to report: "Anatomic alterations which were of minor importance, such as those related to physiologic involutions and atrophy, chronic inflammations, and degeneration associated with aging, were not included in the tables of pathologic diagnoses. These lesions had little or no influence on th the 'well-being' or longevity of the animal, and they were unrelated to the test compound...." (emphasis added). Only "important" lesions - these related to cause of death of test animals, chronic lesions related to test compound, and neoplastic lesions are "diagnosed and tabulated." (Rept., p. 10).

We judge this practice (of excluding so-called "minor" autopsy findings from the report) as undesirable, at best, and, at worst, unacceptable; since certain omitted findings might be judged toxicologically significant by other scientists.

Results. Both M and F rats in top-dose (1,600-ppm) groups in both studies grew less well (e.g., 10%) during first 3-4 months. Other test rats did not consistently lag behind controls. Food consumption values are not included; therefore, one cannot pick out any cause of reduced body-weight gain.

There was no effect on mortality.

There was no effect on hematologic or blood chemistry or urine values. The commonly noted protein in urine is ascribed to glomerulonephritis, which occurred in both test rats and controls.

Males in top-dose group had higher kidney/body weight ratios. Gross and microscopic findings, including incidence of neoplasms, show little, if any, effect of test compound, judged by perusal of the summary tables provided. A previously found lesion (in 90-day rat feeding at 2,500 ppm), vacuolization of pancreatic acinar cells, occurred infrequently in these studies.

Results of assay of test diets show good agreement with theoretical content of test compound. This includes diets "aged" the time they would have been in the study,—one week.

Two-year mouse feeding studies (M-9153 and M-9163), tebuthiuron, by G. C. Todd et al., Lilly Research Labs., Nov., 1976, Sec. C, this PP, Ex. 3. 20717

Method. Two identical 2-yr feeding studies were carried out on Harlan ICR mice, using technical (97%) tebuthiuron (Lot no. B30-23-149). Mice (3-4 wks old; 16-26 g in wt) were housed 4 to a cage.

Design of the studies is nearly identical to that of the rat studies (above). Exceptions: Food consumption was not measured; hematologic and blood chemical determinations were made only at 2 years; no urinalysis was done; kidney and adrenal were weighed together, as was uterus with ovary, and neither prostate nor thyroid-parathyroid was weighed.

Again, so-called "minor" lesions are not tabulated (report, p. 10). Again, the practice is judged not desirable-to-unacceptable.

Results. Test compound had minimal effect (decrease) on body-weight gain and no apparent effect on mortality hematologic values, or blood chemical values. Inspection of tables of microscopic findings reported indicates that no important treatment-related, chronic signs of disease occurred, and that incidence of neoplasms is roughly the same throughout control and test groups.

Assayed content of tebuthiuron in diets, both fresh and those aged one week, agrees well with the theoretical.

Addendum to the two rat and mouse long-term studies:

Combined tumor incidences of the two rat studies were evaluated statistically, as were those of the two mouse studies. Reference is: Young, S. A., Analysis of Tumor Incidence in Chronic Toxicity Tests. Presented at the ASA Meeting, Boston, 8/22-8/27/76.

Results are presented below.

Mouse (Studies M-9153 and M-9163)

		Incidence of Neoplasms				
		Percent in Diet				
Neoplasm	Sex	0.0	0.04	0.08	0.16	"Z" value
Benign	Male	0.32	0.30	0.33	0.25	-0.71
"	Female	0.19	0.19	0.27	0.27	1.40
Malignant	Male	0.41	0.34	0.22	0.34	-1.24
"	Female	0.85	0.63	0.67	0.69	-1.97

Results are said to show statistically significant decrease in malignant tumors in females and to provide no evidence that tebuthiuron caused an increase in tumor incidence.

Analagous calculations for rat studies (R-603 and R-613) gave:

Neoplasm	Sex	Percent in Diet 0.0	0.04	0.08	0.16	"Z" value
Benign	Male	0.37	0.13	0.26	0.24	-1.13
"	Female	0.58	0.74	0.60	0.64	0.15
Malignant	Male	0.11	0.19	0.09	0.09	-1.07
"	Female	0.15	0.15	0.09	0.15	-0.40

Author's Comment:

"The Z-statistic should be distributed normally with a mean of zero and a variance of one....None of these (four) tests obtain statistical significance at the 5% level."

Rat reproduction study (3-generation, 4-litter) with tebuthiuron, by G. C. Todd et al., Toxicol. Div., Lilly Research Labs., April, 1975, this PP, Sec. C, Bk. 1.

Method. Groups of 20 rats/sex/group each received 400 or 800 ppm tebuthiuron technical (Lot B30-23-149) for three generations. Thirty rats/sex were controls.

The first Fo parental breeding trial produced poor progeny survival in all groups (and comparable weight of pups); so Fo rats were bred again.

The procedure varies from a "standard" one in that only 4 litters (not 6) were produced; litters were not reduced to 10 pups at day 4 (or 5); food consumption and growth of parental generations were determined; and any parental rat which died was examined grossly and microscopically (unless cause of death was apparent); growth and survival of pups at days 0, 1, 7, 14, and 21 was determined; in calculating mean pup weights, that of each litter was used as the sampling unit. Finally, fertility index (% of females pregnant of those mated); gestation-survival index (proportion of live-born); and 1-day, 7-day, 14-day, and 21-day survival indices (proportions of live-born pups that survived on those days) were calculated for each dietary level of each mating trial.

Test compound was given to Fo rats for 79 days; to F1 rats, 65 days; and to F2 rats, only 35 days. No reason for the different time-periods is given. Nor is it clear whether females received test chemical during pregnancy and lactation. These points should be clarified by Petitioner.

Mary L. Gunderman 5-31-77

33

EVALUATION

Significant new submissions comprise rat and mouse 2-yr feeding, rat reproduction, and rabbit teratologic studies on technical tebuthiuron.

Tebuthiuron is not teratogenic in the rabbit at up to 25 mg/kg BW; although this level caused dams to gain less weight and reduced the fetal birth-weight. A lower dose, 10 mg/kg, did not affect parental or fetal (birth-) weights.

In rats, tebuthiuron, as tested, showed adverse effect on reproduction only in consistently depressing pre-weaning growth of pups at both 400 and 800 ppm. (It also inhibited parental growth.) Thus neither test level is "no-effect." However, it is not clear whether female test rats received tebuthiuron throughout the periods of pregnancy and lactation. Nor are details of both the examination and the gross and microscopic findings on F3a pups given. Nor does the test provide acceptable procedure for three generations; since F2 rats received tebuthiuron in the diet for only 35 days (compared to a minimum required 60 days). For these reasons, the study is judged unacceptable

A "no-effect level" for the rat 2-yr feeding studies cannot be set, based on present information; although 1,600 ppm is shown to be an "effect level," having caused depressed growth and, in males, increased kidney wt/body wt values. The studies are not acceptable as oncogenicity or chronic studies; since description (tabulation) of all microscopic findings is required - not only those judged "important" or "related to test compound administration" - before they can so qualify. Likewise, the mouse studies are not acceptable for the same reason.

Dr. E. Long, Pathologist in TB, details requirements as follows: Gross. Descriptions, with weights and/or measurements, when appropriate, of all lesions in individual animals. Summaries of recurring lesions are acceptable. Microscopic. Descriptions and diagnoses of all lesions in individual animals. Summaries are acceptable, but important individual variations should be noted. Grading of severity of common lesions, such as chronic nephritis, testicular atrophy, myocardial fibrosis and necrosis, hepatic fat, hepatic bile duct proliferation, splenic hemosiderin, pneumonitis, etc. Grades are essential for individual animals and treatment groups, with the sexes treated separately.

In any case, mutagenicity data on tebuthiuron must also be supplied to support safety of these requested tolerances (mem. title).

Finally, we defer to CB as to whether chemical analysis of the formulation for possible presence of nitrosamines is required. (Tebuthiuron, a secondary amine, is theoretically capable of forming same.)

For the record, "no-effect" in 90-day rat and dog feeding studies on tebuthiuron were set at 1,000 and 500 ppm, respectively, by Mr. D. Ritter (2/21/75, PP No. 5G1562).

M. L. Campfe, Ph.D 5/31/77
TB/RO

51

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: August 1[illegible], 1978

SUBJECT: Tebuthiuron, tolerances requested in PP No. 7F19[illegible], Petitioner's ltr. of [illegible]/78, replying to EPA reject letter of 12/1/77, TB comments on; [illegible]

FROM: TB/HED, [illegible], Ph.D.

TO: Mr. R. J. Taylor, PM (25), RD

005822

PP No. 7F19[illegible]

Elanco Prods. Co., Eli Lilly
Indianapolis, IN [illegible]

EVALUATION: We note, CB has listed deficiencies with regard to residue chemistry data and has raised the question of possible nitrosamine content of tebuthiuron (CB memo of Mr. A Smith, 10/13/77, this PP). We await CB's evaluation of any response Petitioner may make and satisfaction of TOX deficiencies not presently alleviated (see below) - i.e., (1) Need for review of pathologic findings of Petitioner in (two each) 2-yr rat and mouse feeding studies on tebuthiuron by EPA pathologist and (2) Lack of "no-effect level" in rat reproduction study done on tebuthiuron, before making final conclusions on safety to human beings of tolerances requested in this PP. As to adequacy of mutagenicity data, we have no final comment at this time, pending Agency decision as to exactly what types will be required to support a tolerance.

Petitioner's reply to each point of the 12/1/77 reject letter <u>for this PP</u> (which we give also) and our commentary given below:

<u>Point 1</u>: The accounts of gross and microscopic findings in the 2-yr rat and mouse feeding studies are incomplete.

Petitioner claims Drs. [illegible] and [illegible] Long, "...did not have access to the full submission in which gross and microscopic findings were listed by individual test animal.... (they) were going to obtain (them),...."

<u>Comment</u>. This reviewer <u>did</u> see (and commented on) the detailed pathologic findings in the 2-yr rat and mouse studies (cf. our 5/31/77 memo, this PP). In consultation with Dr. Long, they were judged not acceptably detailed (as stated in the 5/31/77 memo). However, it is correct that Dr. Long [illegible] at the 2/9/78 conference to review these pathologic findings in detail. Her untimely [illegible] has prevented this, and, therefore, they are not [illegible] evaluated [illegible]. [illegible] deficiency [illegible] of the 12/1/77 [illegible] to the [illegible] unalleviated.

<u>[illegible]</u>: [illegible] female rats receive test diet throughout pregnancy and lactation?

[illegible], "[illegible] containing the test [illegible] for the entire study."

<u>Comment</u>. We accept this statement (clarification). Point 2, sentence [illegible] (PP 7F19[illegible], 12/1/77 ltr.) deficiency is now alleviated.

BEST AVAILABLE COPY

[illegible]: Details of exa[illegible]ion and findings on F3a rats were not supplied.

Petitioner now submits [illegible] of such findings, Report [illegible], Accession No. [illegible]7101, Addendum, [illegible] in the F3a Offspring, A Multi-generation Reproduction Study with [illegible] in the Rat by [illegible] Todd, [illegible], [illegible] Owen, [illegible] Gossett and [illegible] Morton, Lilly Research Laboratories, April, 1975, Addendum Date, February, 1978.

Gross examination and microscopic examination were made of following tissue preparations from one male and one female of each of the F3a litters, ca. 65 individual pups: Spleen, lymph node, skeletal muscle, lung, heart, salivary gland, liver, pancreas, stomach, duodenum, ileum, adrenal, thyroid and thymus. The examiner was "a ACVP certified pathologist with experience in evaluating the offspring of multigeneration rat studies."

Except for some findings in two pups (related to hydronephrosis) and a different finding in one pup (abscess of urinary bladder), no adverse effects are reported for gross or microscopic assay.

We [illegible]. This deficiency (Point 2, sentence 4 of the 12/1/77, PP reject letter, is now alleviated.

[illegible]: The rat reproduction study does not provide a "no-effect level."

Petitioner [illegible]: The only compound-related finding was a reduction in body weight gain. This effect was adequately [illegible] in the [illegible]-mo. rat study (R-[illegible] and a [illegible] subacute rat study (R-72). The test compound had no effect on reproductive parameters.

[illegible]. [illegible] depressed body-weight gain in pups prior to weaning is exactly the "[illegible]" to which we referred. We hold that ability of the dam to provide [illegible] nourishment of offspring during the nursing period is a "parameter of reproduction." Whether inferior growth of pre-weanlings receiving test compound is due to an "antimetabolite" effect, or to some other mechanism, is judged immaterial - it is still depressed growth and, we believe, an adverse aspect of reproduction.

Thus, the [illegible]/78 response of Petitioner relating to the PP does not alleviate the deficiency of the 12/1/77 reject letter expressed in Point 2, sentence 1.

Point 3: Mutagenicity data on tebuthiuron are needed.

Petitioner responds by submission of data from both an Ames-type test on micro-organisms and a dominant-lethal study in rats to show tebuthiuron is not mutagenic. Results appear to support the claim of non-mutagenicity of tebuthiuron. However, we defer detailed review of these data to a later date.

UNITED S.ATES ENVIRONMENTAL PROTECTIC AGENCY

366AA

DATE: April 24, 1979

005822

SUBJECT: Tebuthiuron, submission of 2/5/79 regarding PP No. 7F1925 and Spike 20P (Graslan 20P), TB/HED comment on, addendum to our memo of 4/12/79

FROM: TB/HED H L Rowitz, 4/24/79

TO: Mr. R. Mountfort, PM (25)

PP No. 7F1925
(also, Spike 20P, 1471-RNO)

Elanco Products Co., Div. Eli Lilly
Indianapolis, Ind. 46205

In conversation with Dr. A. Gross, TB/HED Branch Chief, it was agreed that "deficiency 1" of our 8/18/78 TB review (relating to presumed need for review of pathologic findings of Petitioner in 2-yr rat and mouse feeding studies on tebuthiuron by an EPA pathologist) is now alleviated.

It was also agreed that the need to establish a definitive "no-effect level" for tebuthiuron in (the 3-generation) rat reproduction study is not alleviated. The deficiency remains.

Petitioner is requested, therefore, to carry out such additional study as will establish, definitively, a "no-effect level" for tebuthiuron on reproduction in the rat.

Lacking a "no-effect level" for tebuthiuron on reproduction in the rat, TB is unable to define an allowable daily intake on which to evaluate safety of permanent tolerances for tebuthiuron. Accordingly, TB cannot recommend for the permanent tolerances asked for in the revised Section F, this petition.

4/27/79

54

EPA FORM 1320-6 (REV. 3-76)

Reviewed by: D. Ritter, Toxicologist DR 3-13-87
Section I , Tox. Branch (TS-769C)
Secondary reviewer: R. Bruce Jager, Section Head 3/13/87
Section I , Tox. Branch (TS-769C)

80358-3
Rat05822

DATA EVALUATION REPORT

STUDY TYPE: Teratology Study, Rat. TOX. CHEM. NO. 366AA

ACCESSION NUMBER: MRID NO.: 20803

TEST MATERIAL: N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea.

SYNONYMS: Tebuthiuron; Lilly Compound # 75503; EL-103.

STUDY NUMBER(S): R-632.

SPONSOR: Eli Lilly and Company, Greenfield, IN.

TESTING FACILITY: Lilly Research Laboratories, Greenfield, IN.

TITLE OF REPORT: Rat Teratology Study With (EL-103).

AUTHOR(S): G. C. Todd, J. K. Markham, et al.

REPORT ISSUED: September, 1972.

CONCLUSIONS: No evidence of teratogenic effects.

Classification: CORE - Supplementary.

Special Review Criteria (40 CFR 154.7) None.

A. MATERIALS:

See the review of D. Ritter, 2-21-75, copy attached.

The study is considered to be supplemental by today's standards because only summaries, but no detailed analytical data accompanied the submission. These should include:

1. Individual dams' body weights.

2. Individual litter data

In addition, the test material was offered in the diet, rather than being given by gavage as recommended.

These deficiencies render this study "Supplemental". This classification could be upgraded by submission of the missing detailed data and by offering an explanation as to why the material was fed rather than being given by gavage.

-5-

Clinical chemistry findings indicated increased BUN in the 2000 ppm females; in addition, this group exhibited increasing levels for Alkaline phosphatase, up to four-fold over that of controls. Levels of this parameter had returned to normal at the terminal sampling. The 2000 ppm males likewise demonstrated this finding. There were no urinary abnormalities.

1000 ppm females and males demonstrated increased thyroid/body weight ratios and the 2000 ppm females also showed increased spleen ratio.

Histopathological findings were negative for adverse effect of EL-103.

Conclusions:

The systemic NEL for feeding of EL-103 to dogs for three months is considered to be 500 ppm on the basis of increased thyroid ratios, increased Alkaline phosphatase values and increased BUN in test animals.

C. Rat Teratology Study (R-632)

Methods:

Pregnant Harlen rats were offered diets containing 0, 600, 1200 or 1800 ppm EL-103 during gestation days 6-15. Pups were obtained by Ceasarian section and were examined for weight, sex distribution, external visceral and skeletal anomalies. Uteri and ovaries were examined for corpora lutea, distribution of fetuses, resorptions and litter size.

Approximately a third of the fetuses in each litter were fixed in buoin's solution for visceral examination and the remainder were cleared for skeletal examination.

Results:

Abnormalities of somatic architechture were few in number and low in severity and were not dose related. Body weights and other paramaters were not adversely affected.

Conclusions:

EL-103 is not a teratogen in rats at up to 1800 ppm when given in the diet during days 6-15 of gestation.

Reviewer: David L. Ritter /s/ David Ritter 2-21-75
2nd Reviewer George E Whitmire DVM /s/ GEW 2-21-75

56

DER 2-27-87

83-4 005822

Rat

Reviewed by: D. Ritter
Section 1 , Tox. Branch (TS-769C)
Secondary reviewer: R. Bruce Jaeger 2/27/87
Section 1 , Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Two Generation Reproduction, Rat TOX. CHEM. NO. 366AA

ACCESSION NUMBER: 246374 MRID NO.: 0090108

TEST MATERIAL: N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea.

SYNONYMS: Tebuthiuron; Lilly Compound # 75503; EL-103.

STUDY NUMBER(S): R03780; R08780.

SPONSOR: Elanco Products, Indianapolis, IN.

TESTING FACILITY: Lilly Research Laboratories, Greenfield, IN.

TITLE OF REPORT: A Two Generation Reproduction Study with Tebuthiuron (Compound 75503) in the Wistar Rat.

AUTHOR(S): E.R. Adams, N. V. Owen and J. A. Hoyt.

REPORT ISSUED: November, 1981.

CONCLUSIONS: Reproductive NOEL ≥ 400 ppm (20 mg/kg bwt./day);
Systemic NOEL < 100 ppm (5 mg/kg bwt./day).

Classification: CORE-Guideline.

Special Review Criteria (40 CFR 154.7) None identified.

A. MATERIALS and STUDY DESIGN:

See the Review of Dr. M. L. Quaife of 2/23/82 (copy attached).

Briefly, Harlan rats were offered diets containing 0, 100, 200 or 400 ppm (5, 10 or 20 mg/kg bwt./day) technical Tebuthiuron through two generations of offspring (MRID 90108).

B. RESULTS AND CONCLUSIONS:

Dr. Quaife determined that there were no adverse effects except that F1 females in the pre-mating phase showed a lower rate of body weight gain in the 200 and 400 ppm groups. No adverse effects were reported on reproductive performance at any level. The NOEL for reproductive effects is > 400 ppm (20 mg/kg bwt./day). She requested that the Company provide statistical information relating to parental and offspring body weights.

57

The data were subsequently received and evaluated in the review of Dr. G. W. Robinson, who concluded that the systemic NOEL based on pre-mating body weights and weanling litter weights was less than 100 ppm and the reproductive NOEL was greater than 400 ppm (review of EPA Reg. # 1471-109, 8/25/82, copy attached).

005822

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FEB 23 1982

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM:

DATE: February 11, 1982

SUBJECT: Tebuthiuron technical, repeat rat reproduction study, Accession No. 246374, TB/HED comments on.

FROM: Mary L. Quaife, Ph.D. MLQ 2/11/82
Toxicology Branch/HED (TS-769)

TO: PM, Mr. R. Taylor
Registration Division (TS-767)

EPA Reg. No. 1471-109
(TB) Caswell No. 366AA

E. Lilly and Company
Indianapolis, Indiana 46285

CONCLUSIONS:

1. The study (preliminary review of which is attached) is judged to conform adequately with submitted and approved (4/17/80) protocol for it.

2. However, in order to complete our review and interpretation of the study, TB/HED requests following information of E. Lilly and Company:

"A. Show: The model for ANOVA or ANCOVA with your rationale for the model; the expected mean square errors; the tables showing the computed mean square errors with associated degrees of freedom; and the means, the variance-covariance matrices, and other pertinent EDP outputs associated with the significance statements relating to absolute body weights of the parents and the weanlings of the F_1 and F_2 generations.

B. i. Why is the Bonferroni adjustment applied to results of Dunnett's "t" test?

ii For which comparisons will the inference of statistical significance be materially affected if not used (i.e., which comparison related to body weight will become statistically significant at $p \leq 0.05$)?"

005822

NEW TOXICOLOGY:

"A two-generation reproduction study with tebuthiuron (compound 75503) in the Wistar rat," by E. R. Adams, M. V. Owen, and J. A Hoyt, Eli Lilly & Co., Greenfield, Ind. Dated, November 1981, Acc. No. 246374; Lilly Nos. RO5780 and RO8780.

Test compound. Tebuthiuron (N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea) technical, Lot No. 00880-11-1, X-35920, analytical characterization according to attached pages, Appendices C-1 to C-3, this report (copies of), pp. 9-11 of this memo.

Procedure. Groups of 25M and 25F Wistar rats (Harlan Industries, Cumberland, Indiana) each received 0, 100, 200, or 400 ppm test compound in the diet (Purina mash) for 101 days (Fo rats) or 124 days (F1 rats) and then for a further period sufficient to mate and rear (ca. 9-10 weeks apart) two successive litters of young to 21 days of age. F1a rats were parents of the F2 offspring.

At the start of feeding tebuthiuron, Fo rat males weighed 100 g and females 90 g (mean each), and F1 rat males and females were ca. 5 wks old.

Prior to mating, all rats were weighed weekly. Males were weighed monthly, thereafter, and females were weighed on the day a copulatory plug was found; on gestation day 20; and on postpartum day 21. Progeny were weighed individually on postpartum days 1, 4, 7, 14, and 21. Rats were culled to 10 per litter on day 4 - with equal numbers of each sex being left, if possible - by a random procedure (described in the report).

During growth, rats were observed daily for general condition, and they were examined more closely each week. Food consumption was measured weekly when rats were weighed, and cumulative efficiency of food utilization was calculated. Bred F's were observed near parturition and pups, when weighed.

Diet assay having shown tebuthiuron to be stable that long, diets were prepared either weekly or every two weeks. Samples of each diet were analyzed for tebuthiuron content at beginning of growth of each parent generation and at termination of the study. Rats received diet and water (chlorinated city water) ad lib.

Sperm morphology and testes of 10 Fo males/dose-group were evaluated microscopically after the second breeding period. At the end of the study, ten F1 adults/sex/dose-group were examined grossly and following tissues taken for microscopic evaluation: Kidney, liver, heart, lung, spleen, thymus, lymph node, salivary gland, pancreas, stomach, duodenum, jejenum, ileum, colon, ovary, uterus, adrenal, thyroid, testis, prostate, skin, mammary gland, skeletal muscle, and urinary bladder. Five weanlings/sex/dose-group of both F1a and F2a progeny were similarly examined, grossly and microscopically.

Gestation length was determined, and numbers of live and stillborn in each litter and number and condition of surviving progeny on postpartum days 1, 4, 7, 14, and 21 were determined for all offspring. Sex of each pup surviving to day 21 was determined (as was that of both culled and remaining progeny on day 4).

Following values were calculated for each dose-group and generation: Fertility index - proportion of females that were pregnant; gestation-survival index - proportion of newborn pups that were alive; survival index - proportion of offspring that survived to 1, 4, 7, 14, and 21 days; and mean number of offspring raised to weaning (day 21)/pregnant female.

005822

Statistical comparisons of mean body weight; body weight gain; food consumption; and efficiency of food utilization were each made. Maternal body weights; gestation survival; liveborn litter size; progeny survival; and mean progeny weight (per litter) on postpartum day 21 were similarly evaluated, i.e., by Dunnett's two-tailed "t" test, with use of a Bonferroni "t," where appropriate. Chi-square contingency tables were used to evaluate fertility data, and statistical significance was set at $p \leq 0.05$.

Report states, in selecting F1a weanlings as parents of F2 rats, representatives of all available litters were included. Nor were individuals of poor physical condition or which weighed less excluded. Weanling selection from within a litter was based on a random number system.

Also, in second breeding trials in Fo and F1 generations, adult females failing to deliver were killed and examined for evidence of pregnancy. All remaining rats - Fo and F1 adults after second breeding trials; progeny culled on postpartum day 4; and weanlings not selected to continue the study - were given terminal eye and physical examinations and killed with CO_2 gas.

A diagram of plan of this study is reproduced on p. 8 of this memo.

Results.

Diet Assays. Mean values (only) for each dose-level diet for the three intervals sampled show good agreement between theoretical and found content of tebuthiuron, the largest difference in one diet being 40 ppm (160 vs. 200) or -20%.

Actual tebuthiuron intake. Time-weighted average tebuthiuron intake for each group - in order, from controls to highest dose-level - was 0, 7, 14, or 28 mg/kg body weight/day. Values are for (Fo, F1) rat pre-mating phases.

Mortality of parents and gross findings. No Fo rats died. Four high-dose rats, one low-dose rat, and one control in the F1 generation died, - apparently of causes unrelated to test compound.

Physical signs. No physical signs shown were judged related to treatment.

Food consumption and cumulative efficiency of food utilization. Tables show beginning body weight, body weight gain, and efficiency of food utilization for Fo and F1 rats during pre-mating periods - mean values/sex/dose-level:

Ppm TBZ in diet	M body wt at start, g	M body wt gained, g	M mean E.F.U.	F body wt at start, g	F body wt gained, g	F mean E.F.U.
	Values for Fo rats, 25/sex/dose-level - 98 days					
0	103.4	440.0	17.4	93.4	265.0	13.3
100	101.2	461.0	17.6	88.5	265.9	13.7
200	99.4	460.3	17.5	87.1	257.0	13.2
400	89.1	442.9	17.3	89.5	251.1	13.1
	Values for F1 rats, 25/sex/dose-level* - 128 days					
0	151.4	490.2	12.6	133.7	269.3	10.3
100	152.0	472.3	13.3	125.3	272.3	10.4
200	144.2	484.7	13.8	121.4	250.4	9.9
400	144.5	472.8	13.1*	118.2	232.5**	9.0*

* Different for 100-ppm males, i.e., 24/sex/dose-level for them.
** Differs from control ($p \leq 0.05$)

61

005822

There were no treatment-related variations in mean daily food consumption during the respective Fo and F1 pre-mating periods.

Mean cumulative efficiency of food utilization (E.F.U.) of Fo test rats of both sexes did not vary from control values during the 98 days it was measured. High-dose (400-ppm) F1 rats had lower ($p \leq 0.05$) E.F.U. near the end of 124 days' (total) feeding (males) or from day 98 on (females); while E.F.U. of F1 females at 200 ppm showed borderline depression.

Body weight of adult rats. Significantly ($p \leq 0.05$) depressed mean body weights during pre-mating period were shown by female F1 rats at both 200 and 400 ppm, days 14 through 124 (i.e., virtually through the entire period). Respective day-124 mean body weights, with standard deviation, are shown below, as are corresponding values for controls and 100-ppm F1 females:

PPM TBZ in Diet	Mean body weight of F1 females at 124 days (g)	Standard deviation
0	403.4	± 59.5
100	397.6	± 39.9
200	371.8*	± 38.4
400	350.7**	± 33.3

* P ≤0.05, Dunnett's two-tailed t test, significance of difference from control.
** P ≤0.01, Dunnett's two-tailed t test, " " " " "

[As can be seen from table on preceding page, mean body weight gain during this period was significantly depressed in female F1 rats at 400 ppm and moderately, but not significantly, depressed in those at 200 ppm.]

Although the report notes (correctly) that the depression in mean F1 female weights in the middle and high dose groups continued throughout the two breeding trials, we do not find particular significance in this fact; since E.F.U. data are lacking and since weight gain would be expected to vary with number of fetuses carried by the pregnant rat.

Statistically significant differences of test rat values from corresponding control values were not seen for mean body wts of treated Fo parental male and female rats and F1 parental male rats during pre-mating periods or ensuing breeding trials.

Live-born litter size. Table below shows mean live-born litter size (and S.E.):

Rat progeny	Mean number liveborn per litter and S.E.			
	ppm tebuthiuron in diet			
	0	100	200	400
F1a	11.9 (1.0)	13.3 (0.7)	12.9 (0.7)	12.5 (0.7)
F1b	10.2 (1.2)	12.3 (0.9)	10.6 (0.8)	12.4 (0.8)

(continued)

6.

Rat progeny	Mean number liveborn per litter and S.E. ppm tebuthiuron in diet			
	0	100	200	400
F2a	10.5 (1.1)	11.0 (1.2)	9.6 (0.9)	13.3 (0.6)
F2b	9.9 (1.3)	11.8 (1.2)	11.6 (1.1)	12.7 (0.9)

In general, treated females had larger litters than control females, but differences are said not to be statistically significant.

Fertility. Fertility of control rats appears low, fertility indices for the four litters (F1a-F2b, inclusive) varying from 48 to 68%. No reason is given for this. However, in all cases, test litters had higher mean fertility indices (varying from 64 to 96% for the three dose-levels of F1a-F2b litters, inclusive) than corresponding controls.

Gestation length. Mean gestation lengths were similar in all test groups, varying between 21.9 and 22.5 days.

Progeny survival. Mean gestation survival of all rats - test and control - was 93%, limits being 83 and 98%. Survival to 21 days is said to have varied from 76 to 100%. There was no effect of test compound on survival of offspring.

Sex distribution of progeny. Sex distribution of survivors was determined only on day 21. It was not affected by treatment and varied between 45 and 61% males.

Mean number of offspring surviving to 21 days of age per pregnant female. Mean number of offspring at day 21 per pregnant female varied between 6.3 and 8.1 for control groups in the four (F1a-F2b, inclusive) litters. Corresponding test animal values varied between 6.1 and 8.6. Thus, test and control values cover similar ranges.

Condition of progeny. No findings in test rat offspring are ascribed to tebuthiuron, either gross or microscopic (latter in 5 rats/sex/dose-level of F1a and F2a weanlings which were examined histopathologically). One high-dose pup had cleft palate and three pups within a single litter in the low-dose group had multiple anomalies, including rudimentary tail, imperforate anus, varus hind limbs, missing ribs bilaterally, missing vertebrae, and fused vertebrae. Due to low incidence and lack of dose-response, findings are not considered treatment-related (this reviewer agrees).

Adult rat examination results. No tissue alterations found in the F1a adults examined histopathologically are ascribed to treatment with the test chemical. Testes from control and test rats, Fo parental rats, which were examined microscopically were normal. Sperm morphology, also, was normal in all treated rats examined, i.e., Fo rats.

005822

Body weights of offspring. Below are given mean progeny weights at day 1 and at day 21 of all rat progeny (with S.E.).

Ppm TBZ in the diet	Number of pregnant females	Mean body weight (g) ± S.E. of progeny on postpartum day 1	Mean body weight (g) ± S.E. of progeny on postpartum day 21	Progeny of litter
0	17	6.9 (0.2)	45.3 (1.6)	F1a
100	21	6.5 (0.2)	42.7 (1.7)	"
200	18	6.4 (0.1)	44.2 (2.5)	"
400	23	6.8 (0.2)	41.9 (1.7)	"
0	14	6.9 (0.1)	45.6 (1.7)	F1b
100	20	6.5 (0.2)	43.1 (1.2)	"
200	17	6.5 (0.1)	43.4 (1.8)	"
400	24	6.6 (0.1)	42.0 (1.1)	"
0	12	6.9 (0.3)	46.1 (2.0)	F2a
100	16	6.5 (0.2)	41.1 (1.6)	"
200	21	6.4 (0.2)	44.5 (1.8)	"
400	17	6.3 (0.1)	43.6 (1.0)	"
0	14	6.8 (0.2)	45.9 (2.2)	F2b
100	19	6.4 (0.2)	42.7 (1.4)	"
200	19	6.8 (0.2)	43.5 (1.7)	"
400	20	6.6 (0.1)	42.3 (1.2)	"

Without exception, mean 21-day body weights of test rat offspring are lower than corresponding controls. However, significant differences do not occur. (These remarks pertain to the table of preceding page of memo.)

005822

Petitioner has calculated the mean 21-day body weights of test and control rat progeny in which 10 pups/litter were maintained "through postpartum day 21," presumably, meaning from day 4 (when litters were culled to 10 if necessary) to day 21. "Pooled means from the four breeding trials using the litter as the sampling unit" are given as 41.9, 41.4, 41.5, and 41.9 g, respectively, for control, low-dose, mid-dose, and high-dose offspring of the combined F1a, F1b, F2a, and F2b litters.

[In sum, with exception of retarded growth reported by Petitioner for dietary levels, 200 and 400 ppm, in this study, adverse effects are not reported.]

COMMENT:

This study review is incomplete. We need to be sure that proper statistical evaluation of parental body weights (or growth) prior to mating and, also, of weanling litter weights (and growth) is made. See below.

We have consulted our TB/HED Statistician, Mr. Bert Litt, over some questions we have (related to the above) in interpreting study results. He suggests we ask Petitioner for more information about the statistical analysis made on the study, as follows:

"Please answer questions as to how data were statistically analyzed:

A. Show: The model used for ANOVA or ANCOVA with your rationale for the model; the expected mean square errors; the tables showing the computed mean square errors with associated degrees of freedom; and the means, the variance-covariance matrices, and other pertinent EDP outputs associated with the significance statements relating to absolute body weights of the parents and the weanlings of the F1 and F2 generations.

B. 1. Why is the Bonferroni adjustment applied to results of Dunnett's "t" test?

2. For which comparisons will the inference of statistical significance be materially affected if not used (i.e., which comparison related to body weight will become statistically at $p \leq 0.05$)?"

TB/HED withholds further comment on the study, pending receipt of replies to these questions (and TB/HED - Statistician's - evaluation of them).

[We note that correct interpretation of this study is very important. Up to now, we have declined to estimate an allowable daily intake (ADI) for tebuthiuron tech. due to apparent growth inhibition at lowest dietary level previously tested, 400 ppm, - in rat chronic and subchronic feeding trials - and to statistically significantly retarded growth of weanlings (and parents?), at 400 ppm, in previously submitted rat reproduction study. (No long-term dog study is available, on which an ADI might be based.) Therefore, an ADI will rely, presumably, in whole or in part, on the growth "no-effect level" determined for this reproduction study.]

EPA REG. NO. 10550I RIN 0634-93

Page_____ is not included in this copy.

Pages 66 through 69 are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

___✓___ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

005822

Need cover page MRID 20759

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

53-4 Rat 53-4; Rab

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM AUG 25 1982

MRID 20759

TO: Robert J. Taylor, PM #25
Registration Division (TS-767)

THRU: Robert B. Jaeger, Section Head 8/20/82
Review Section #1
Toxicology Branch/HED (TS-769)

SUBJECT: EPA Reg. No. 1471-109, Tebuthiuron; Repeat Rat Reproduction Study. CASWELL #366AA

Registrant: Elanco Products Company
A Division of Eli Lilly and Company
Indianapolis, IN 46285

The registrant has submitted additional information (letter, R.M. Hill, Elanco, 4/28/82) as requested by a previous reviewer (memo, M.L. Quaife, TB/HED, 2/23/82). This statistical information, based on my scientific judgement, provides for adequate interpretation of the rat reproduction study and completion of our review.

Conclusion:

Proper statistical evaluation of parental body weights and weanling litter weights has been made. No adverse effects were reported in this study except a lower rate of body weight gain during the pre-mating period in F_1 females at dietary levels of 200 and 400 ppm of tebuthiuron. Reproduction in animals under study was not affected.

Systemic toxicity NOEL $\geq$ 100 ppm
Reproductive NOEL > 400 ppm

70

Classification: Core-Guideline

005822

George W. Robinson, D.V.M.
Review Section #1
Toxicology Branch/HED (TS-769)

8/24/82

TS-769:ROBINSON:sll:X73710:8/19/82

Reviewed by: D. Ritter 040-2/27/87
Section I , Tox. Branch (TS-769C)
Secondary reviewer: R. Bruce Jaeger 4/13/87
Section I , Tox. Branch (TS-769C)

84-2
Mouse Lymphoma

DATA EVALUATION REPORT

005822

STUDY TYPE: Mouse Lymphoma Assay TOX. CHEM. NO. 365AA

ACCESSION NUMBER: 254573 MRID NO.: 145041

TEST MATERIAL: N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea.

SYNONYMS: Tebuthiuron; Lilly Compound # 75503; EL-103.

STUDY NUMBER(S): 840410 MLA655; 84060MLA655; 840612MLA655.

SPONSOR: Eli Lilly and Company, Greenfield, IN.

TESTING FACILITY: Lilly Research Laboratories, Greenfield, IN.

TITLE OF REPORT: The Effect of TEbuthiuron (Lilly Compound 75503) On the Induction of Forward Mutation at the Thymidine Kinase Locus of L5178Y Mouse Lymphoma Cells.

AUTHOR(S): T.J. Oberly, B.J. Bewsey and G.C. Todd.

REPORT ISSUED: 8/84.

CONCLUSIONS: Tebuthiuron was mildly mutagenic in the assays w/out activation, but not in those with activation.

Classification: Acceptable.

Special Review Criteria (40 CFR 154.7) None exceeded.

PROCEDURES:

See the G. Robinson review of 5/3/85, copy attached.

RESULTS:

See the G. Robinson review of 5/3/85, copy attached.

IV. The Effect of Tebuthiuron (Lilly Compound 75503) on the Induction of Forward Mutation at the Thymidine Kinase Locus of L5178Y Mouse Lymphoma Cells by T. J. Oberly, B. J. Bewsey and G. C. Todd, Lilly Research Laboratories, Studies 840410 MLA655, 840606MLA655 and 840612MLA655; 8/84, Acc. No. 254573.

Test Material:

Tebuthiuron (Lilly compound 75503, EL-103), Lot X-35920, 98.0%.

Positive Control Material:

a. Ethylmethanesulfonate (EMS), for non-activated assay.
b. 3-methylcholanthrene (3MC), for activated assay.

Vehicle Control Material:

All test chemicals were dissolved in reagent grade DMSO.

S9 Microsomal Activation Enzymes:

Supernatant fraction of a 25% liver homogenate from rats treated 5 days prior with a single 500 mg/kg i.p. dose of Aroclor 1254.

Cell Cultures:

$TK^{+/-}$ cells (TK3.7.2C), a subline of the mouse lymphoma cell L5178Y heterozygous for thymidine kinase. Suspension cultures were initiated with stock cells stored in liquid nitrogen and maintained with growth medium.

Test Concentration Selection:

A preliminary toxicity test of tebuthiuron at 8 concentrations ranging from 10 to 5,000 ug/ml was conducted in suspension cultures of L5178Y $TK^{+/-}$ cells with and without metabolic activation. At the same time, a precipitation test of each concentration of tebuthiuron was conducted in medium without cells; all tested concentrations were soluble in the culture medium. Based on these preliminary tests, 8 tebuthiuron concentrations ranging from 100 to 800 ug/ml were selected for the non-activated mutagenicity assay; 8 tebuthiuron concentrations ranging from 10 to 1,000 ug/ml were chosen for the activated mutagenicity assay.

Memo of 2-3-85 George W Robinson

George W. Robinson, DVM /S/ 4-30-85
William L. Burnam /S/ WLB 5-2-85

Non-Activated Assay:

Ten ml of $TK^{+/-}$ cell suspension and 0.1 ml of the appropriate 100x dilution of tebuthiuron were combined and incubated for 4 hr. at 37°C in a roller drum. EMS was added to positive control cultures at a final concentration of 620 ug/ml; DMSO (1%) served as the vehicle (negative) control. Exposed cells were washed twice, resuspended in cell culture medium and incubated in a roller drum for 48 hr. to allow the expression of $TK^{-/-}$ mutants. Each culture was serially diluted to a final suspension of 100 cells/ml in growth medium. One ml of this suspension (100 cells) was added to 30 ml of non-selective agar cloning medium and incubated for 12 days at 37°C. This medium supported the growth of both $TK^{+/-}$ and $TK^{-/-}$ cells. One ml of a cell suspension (500,000 cells) was added to 30 ml of selective agar cloning medium containing trifluorothymidine (TFT) for the selection of $TK^{-/-}$ mutants. All agar- cell cultures were plated in triplicate.

Activated Assay:

The S9 enzyme mixture was diluted in cell culture medium prior to use. Ten ml of $TK^{+/-}$ cell suspension (containing S9) and 0.1 ml of the appropriate 100x dilution of tebuthiuron were combined and incubated for 4 hr. in a roller drum. 3MC was added to positive control cultures at a final dilution of 2 ug/ml; 1% DMSO served as the vehicle (negative) control. All succeeding steps in this assay were identical to those described for the non-activated assay.

L5178Y $TK^{+/-}$ Assay Count:

Viable colonies grown in non-selective agar cloning medium and $TK^{-/-}$ mutants grown in TFT-selective agar cloning medium were counted automatically with an automated colony counter. Large and small colonies were included in the total count and mean numbers of colonies were calculated from triplicate plates.

Criterion for a Positive Response:

"The criterion for a positive response for chemical-induced mammalian cell mutation was a dose dependent increase in $TK^{-/-}$ mutation frequency where values for mutation index were two-fold or greater than controls at two successive treatment levels. Furthermore, only cultures showing greater than 10% total survival were included in the final evaluation for a mutagenic response". (p.11).

Results:

Tebuthiuron concentrations of 100, 200, 300, 400, 500, 600, 700 and 800 ug/ml were used in the original non-activated mutagenicity assay. Dose-related cytotoxicity was observed in all treated cultures. Suspension growth in treated cultures as a percentage of that in vehicle control cultures ranged from 13% at 800 ug/ml to 57% at 100 ug/ml; total survival, in the same dose range, was from 13 to 66% of that in vehicle control cultures. A dose related increase in mutation frequency occurred in cultures treated with tebuthiuron as evidenced by mutation indexes of 2.0 and 2.4 at concentrations of 700 and 800 ug/ml, respectively.

In the original activated mutagenicity assay, tebuthiuron concentrations of 10, 100, 200, 300, 400, 500, 750 and 1,000 ug/ml were used. Dose related cytotoxicity was also observed in these treated cultures. There were no surviving cells at 1000 ug/ml. Suspension growth in treated cultures as a percentage of that in vehicle control cultures ranged from 6% at 750 ug/ml to 28% at 10 ug/ml. Cultures treated with 750 and 1,000 ug/ml could not be cloned. Total survival in treated cultures was 12% of vehicle control values at 500 ug/ml to 28% at 10 ug/ml. Mutation frequencies in cultures treated with tebuthiuron at doses from 10 to 500 ug/ml did not differ appreciably from vehicle controls.

The non-activated mutagenicity assay was repeated to evaluate the significance of the increased mutation frequency detected in tebuthiuron treated cultures in the original non-activated mutagenicity assay. Tebuthiuron concentrations of 10, 100, 200, 400, 500, 600, 700 and 800 ug/ml were used in this assay. Excessive toxicity at all treatment levels above 200 ug/ml prevented an evaluation of mutagenicity.

An activated assay was also repeated with tebuthiuron concentrations of 1, 10, 100, 200, 400, 500, 600 and 700 ug/ml. Cytotoxicity was extensive at treatment levels from 400 to 700 ug/ml and contamination was present in cultures treated with 200 ug/ml tebuthiuron. Mutagenicity could not be evaluated.

Assays with and without activation were repeated for a second time at tebuthiuron concentrations of 1, 10, 50, 100, 200, 300, 400 and 500 ug/ml. Dose related cytotoxicity was observed in both assays. Total survival ranged from 22% at 500 ug/ml to 82% at 1 ug/ml in the non-activated assay and from 14% at 500 ug/ml to 108% at 1 ug/ml in the activated assay. Again, in the non-activated assay, a dose related increase in mutation frequency occurred with mutation indexes of 2.0, 2.0 and 2.7 at tebuthiuron concentrations of 200, 400 and 500 ug/ml, respectively. Mutation frequencies in tebuthiuron treated cultures did not differ appreciably from vehicle controls in the activated mutagenicity assay.

Cytotoxicity and high mutation frequencies occurred in positive control cultures treated with 620 ug/ml EMS or 2 ug/ml 3MC in non-activated and activated assays, respectively. Findings for EMS and 3MC were similar in the original and repeated assays.

Conclusion:

The L5178 $TK^{+/-}$ mouse lymphoma cell assay was sensitive to direct acting and activation-dependent mutagens. Tebuthiuron was midly mutagenic in the assays without metabolic activation. In the original non-activated assay, mutation indexes of 2.0 and 2.4 were detected in tebuthiuron treated culture at concentrations of 700 and 800 ug/ml, respectively. Mutation indexes of 2.0, 2.0 and 2.7 occurred at tebuthiuron concentrations of 200, 400 and 500 ug/ml, respectively, in a repeat of the non-activated assay. Mutation was not induced by tebuthiuron in the original and repeat assays with metabolic activation.

Classification: Acceptable

84-2005822

Ames Assay

Reviewed by: D. Ritter DGR 2-27-87
Section I , Tox. Branch (TS-769C)
Secondary reviewer: R. Bruce Jaeger 2/27/87
Section I , Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Ames Assay TOX. CHEM. NO. 366AA

ACCESSION NUMBER: 254573 MRID NO.: 141691

TEST MATERIAL: N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea.

SYNONYMS: Tebuthiuron; Lilly Compound # 75503; EL-103.

STUDY NUMBER(S): 840326AMS655.

SPONSOR: Eli Lilly and Company, Greenfield, IN.

TESTING FACILITY: Lilly Research Laboratories, Greenfield, IN.

TITLE OF REPORT: The Effect of TEbuthiuron (Lilly Compound 75503) On the Induction of Reverse Mutations in Salmonella Typhimurium Using the Ames Test.

AUTHOR(S): M.A. Rexroat and G.C. Todd.

REPORT ISSUED: 4/84.

CONCLUSIONS: Tebuthiuron at concentrations up to 5000 ug/plate did with and w/out activation did not induce point mutations in TA98, TA100, TA1535 TA1537 and TA1538.

Classification: Acceptable.

Special Review Criteria (40 CFR 154.7) None exceeded.

PROCEDURES:

See the G. Robinson review of 5/3/85, copy attached.

RESULTS:

See the G. Robinson review of 5/3/85, copy attached.

005822

MRID 41504

II. The Effect of Tebuthiuron (Lilly Compound 75503) on the Induction of Reverse Mutations in Salmonella Typhimurium Using the Ames Test by M.A. Rexroat and G.C. Todd, Lilly Research Laboratories, Study 840326AMS655, 4/84, Acc. No. 254573.

Test Material:

Tebuthiuron (Lilly Compound 75503, EL-103), Lot X-35920, 98.0%.

Positive Control Materials:

a. N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)
b. 2-nitrofluorene (2NF)
c. 9-aminoacridine (9AmAc)
d. 2-aminoanthracine (2AA)

Vehicle Control Material:

Dimethylsulfoxide (DMSO). All chemicals were dissolved and diluted in reagent grade DMSO.

S9 Metabolic Activation Enzymes:

Supernatant fraction of a 25% liver homogenate from rats treated 5 days prior with a single 100 mg/kg dose of Aroclor 1254.

Bacterial Tester Strains:

Five (5) histidine auxotrophs of S. typhimurium LT-2: strains TA98, TA100, TA1535, TA1537 and TA1538.

Media:

Ames base agar medium was prepared and dispensed into petri dishes which were inverted and kept at room temperature for at least 5 days before use. The top agar medium was prepared just prior to use and contained 0.05 mM L-histidine and 0.05 mM biotin.

Memo dtd 5-3-85

George W. Robinson

George. W, Robinson, D.V.M. /S/ 4-30-85

William L. Burnam /S/ 5-2-85- WLB

Toxicity and Precipitation Tests:

A preliminary toxicity test of tebuthiuron at 8 concentrations ranging from 5 to 5000 ug/plate was conducted using Salmonella strain TA100 with and without metabolic activation. A precipitation/solubility test of the same 8 concentrations of tebuthiuron was also conducted, excluding the bacterial tester strain, with and without metabolic activation. The maximum concentration of the test compound which inhibited the growth of TA100 between 50 and 90% and/or did not precipitate in the top agar after incubation at 37°C for 48 hr. was chosen as the high dose for use in the mutation assay. Five concentrations of tebuthiuron (5,000, 2,500, 1,000, 500 and 100 ug/plate) were selected for use in the assay based on results of preliminary toxicity and precipitation tests.

Bacterial Mutation Assay:

For the bacterial mutation assay without activation, the top agar medium was pre-diluted to contain the same equivalent constituents that were present in the top agar with S9 activation mix in the activated assay. An appropriate dilution of tebuthiuron and the respective bacterial tester strain were mixed with the pre-diluted top agar at 45°C and poured onto a plate containing the base agar medium. The top agar mix was evenly distributed by gentle rotation and allowed to gel for at least 30 min. at room temperature. The 5 selected concentrations of tebuthiuron were plated in triplicate for each tester strain. Triplicate plates were prepared for negative and positive controls and designated tester strains. DMSO was the negative control for all strains. Three compounds served as positive controls as follows: MNNG for strains TA100 and TA1535, 9AmAc for strain TA1537, and 2NF for strains TA98 and TA1538. All plates were incubated at 37° C for 48 hours.

In the bacterial mutation assay with activation, the top agar was not pre-diluted since addition of the S9 activation mix provided the same equivalent constituents that were present in diluted top agar for the assay without activation. An appropriate dilution of tebuthiuron, the respective bacterial tester strain, and S9 activation mix were combined with undiluted top agar at 45°C. This solution was mixed quickly and poured onto a plate containing the base agar medium. Other procedures were conducted exactly as in the non-activated assay except that 2AA served as the positive control for all tester strains.

Revertant colonies on each plate were counted with an automated colony counter which covered about 80% of the total measured area of the plate. Counts were corrected to represent the total plate area and mean counts were derived from triplicate plates.

"Criteria for a Positive Response:

A chemical was judged to have induced a positive response when a dose-related increase in revertants was observed in which the number of revertants exceeded control values by at least 2-fold for at least 2 successive concentrations of the test chemical." (p.12).

Results:

In both non-activated and activated mutagen assays, the numbers of histidine revertant colonies for each Salmonella strain (TA98, TA100, TA1535, TA1537 and TA1538) treated with tebuthiuron were similar to the respective DMSO-treated negative controls. A dose-dependent increase in revertants was observed in appropriate tester strains following treatment with positive controls MNNG, 9AmAc and 2NF. Also, dose-dependent increases in revertants resulted from the treatment of each tester strain with the positive control 2AA. These results verified the sensitivity of the Ames bacterial mutagen assay to both direct-acting and activation-dependent mutagens.

Conclusion:

Tebuthiuron, at concentrations up to 5,000 ug/plate with and without metabolic activation, did not induce point mutations in S. typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538.

Classification: Acceptable

Reviewed by: D. Ritter, Toxicologist. DR 3-3-87
Section I, Tox. Branch (TS-769C)
Secondary reviewer: R. Bruce Jaeger. 3/3/87
Section I, Tox. Branch (TS-769C)

85-1
Rat 005822

DATA EVALUATION REPORT

STUDY TYPE: Milk Transfer of Residues in Rats TOX. CHEM. NO. 366AA 005822

ACCESSION NUMBER: NA MRID NO.: 106081

TEST MATERIAL: N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea.

SYNONYMS: Tebuthiuron; Lilly Compound # 75503.

STUDY NUMBER(S): R13781.

SPONSOR: Elanco Products, Indianapolis, IN.

TESTING FACILITY: Lilly Research Laboratories, Greenfield, IN.

TITLE OF REPORT: Radiocarbon Levels in the Milk of Lactating Rats Given 14C Tebuthiuron in the Diet.

AUTHOR(S): Adams, E.; Magnussen, J.; Emmerson, J; et al.

REPORT ISSUED: January 1982.

CONCLUSIONS: Tebuthiuron is present in the milk of lactating rats after dietary administration.

Classification: Acceptable.

Special Review Criteria (40 CFR 154.7) NA.

A. MATERIALS:

1. Tebuthiuron 14C, batch # X-35920, Purity: 98.0%.

2. Test animals: Species: Rat; Strain: Wistar, in late pregnancy.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned 10 F to the following test groups:

Low Dose	100	ppm
High Dose	200	ppm

2. Compound Administration:

Test Material was mixed in to the feed in appropriate amounts. The initial concentration of labeled material was 1.0 uC/mg.

3. Procedure:

Rats were allowed to deliver their litters, then were placed on the diets containing labeled tebuthiuron for 48 hours.

The rats then received a 10 U/mg ip dose of oxytocin ten minutes before being milked.

The milk thus obtained was diluted with 1.0 ml water and prepared for liquid scintillation counting, and counted in a Packard Tri-Barb Model 3380.

C: RESULTS:

The mean 14C tebuthiuron level in the milk of the lactating rats was found to be 2.7 ppm and 6.2 ppm for the 100 ppm rats and the 200 ppm rats respectively.

D: CONCLUSIONS:

Tebuthiuron and/or its metabolite(s) appears in the milk of lactating rats in a dose-dependant manner following dietary administration.